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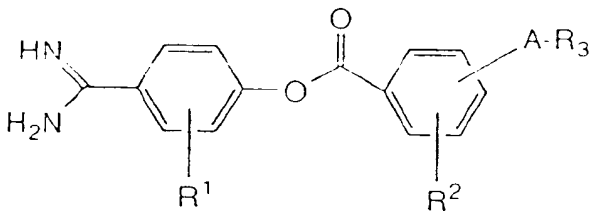
(54) Amidinophenol derivatives as protease inhibitors

(57) The compounds of the formula (IB) and processes for the preparation thereof, leukotrieneB_4 antagonist containing the compounds of the formula (IA) or the formula(IB) as active ingredient, and phospholipaseA_2 and/or trypsin antagonist containing the compounds of the formula (IB) as active ingredient (wherein R^1 and R^2 are -$COOR^4$ etc; A is alkylene etc; R^3 is -CON (R^7)R^8 etc; D ring is the formula (i), (ii) etc; T is NH or oxygen; E is bond, -C (R^{300})=C (R^{400}) -; A_0 is bond, alkylene, oxyalkylene, thioalkylene, (substituted)alkenylene; R is -CON (R^{50})R^{60}, -N (R^{50})R^{60} etc).



(IA)

[Effect] The compounds of the present invention is useful for prevention or treatment of inflammation, allergy, rheumatoid arthritis, inflammatory bowel diseases, psoriasis, nonsteroidal anti-inflammatory agent-induced stomach diseases, adult respiratory distress syndrome, cardiac infarction, hemodialysis-induced neutropenia etc, prevention and treatment of inflammatory diseases, allergic diseases, disseminated intravascular coagulation, pancreatitis or severity in pancreatitis or multiple organ failure.

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Description

The present invention relates to amidinophenol derivatives, processes for the preparation thereof and leukotriene (LT)B_4 antagonist, phospholipase A_2 and/or trypsin inhibitor containing amidinophenol derivatives as active ingredient.

The metabolic pathways by which various compounds are biosynthesized, in vivo, from arachidonic acid as a common starting material is called the arachidonic acid cascade.

Lipoxygenase, for example, 5-lipoxygenase, 12-lipoxygenase or 15-lipoxygenase, respectively, acts on arachidonic acid to produce 5-HPETE, 12-HPETE or 15-HPETE from arachidonic acid.

The above mentioned HPETEs are converted into 5-HETE, 12-HETE or 15-HETE, by converting a peroxy group into a hydroxy group by the action of peroxidase, and 5-HPETE is also converted into LTA_4.

LTA_4 is converted into LTB_4 or LTC_4 by enzymatic reaction (see Biochem. Biophys. Res. Commun., 91, 1266 (1979), Prostaglands, 19(5), 645).

Recently a number of properties of LTB_4 have been revealed.

It is understood that LTB_4 has strong chemotactic and adhesive activity and degranulation activity on leukocytes (see Nature, 286, 264 (1980), Proc. Nat. Acad. Sci. USA, 78, 3887 (1981))

LTB_4 also has strong calcium ionophore action, and attacks various cells, and it is considered to accelerate release of metabolites of arachidonic acid from these cells (see J. Biol. Chem, 257, 4746 (1982)).

High levels of LTB_4 have also been found at sites of various inflammations, for example, rheumatism, spondyl arthritis, gout, psoriasis, ulcerative colitis and respiratory tract diseases, thereby demonstrating that LTB_4 is closely associated with various inflammations (see J. Clin. Invest., 66, 1166 (1980); Lancet II 1122-1123 (1982); J. Invest. Dermatol., 82, 477-479 (1984); Gastroenterology 86, 453-460 (1984)).

It is therefore considered that LTB_4 antagonists are useful as anti-inflammatory agents or anti-allergic agents.

It is known that LTB_4 antagonists are also useful for the treatment of rheumatoid arthritis, inflammatory bowel diseases, psoriasis, nonsteroidal anti-inflammatory agent-induced stomach diseases, adult respiratory distress syndrome, cardiac infarction, allergic rhinitis, hemodialysis-induced neutropenia, anaphase asthma (see the specification of the Japanese Patent Kokai No. 5-239008).

Phospholipase A_2 (PLA_2) is an enzyme which acts on phospholipids existing in cell membranes. It hydrolyzes an ester bond at the second position of the phospholipids. There are two known kinds of PLA_2, membrane-associated PLA_2 and pancreatic PLA_2.

Membrane-associated PLA_2 acts on phospholipids to release arachidonic acid (AA) from the phospholipids. The AA is converted into prostaglandins, thromboxanes and leukotrienes, which are physiologically active substances inducing various inflammatory diseases and allergic diseases.

On the other hand, pancreatic PLA_2 degrades phospholipids and destroys cell membrane, thereby producing lysolecithin having strong cytotoxicity. Recently, much importance has been attached to pancreatitis, severity in pancreatitis and multiple organ failure induced by this destructive activity on cell membrane.

It is also reported that membrane-associated PLA_2 is also concerned with these diseases.

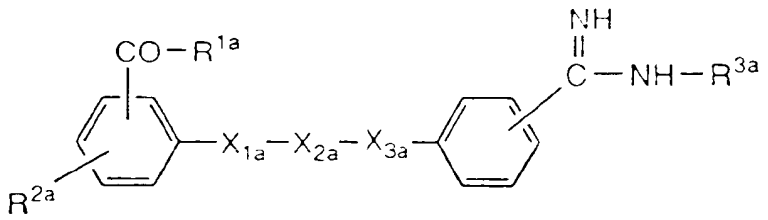
Accordingly, the inhibition of PLA_2 leads to the suppression of the release of AA, a precursor of various physiologically active substances, and therefore, it is considered to be useful for the prevention and/or the treatment of various inflammatory and allergic diseases. Furthermore, it is considered to be useful for the prevention and/or the treatment of pancreatitis, severity in pancreatitis and multiple organ failure due to the inhibition of the destructive activity on cell membranes.

It is also known that the inhibition of various proteases such as trypsin, plasmin, thrombin and kallilrein, especially trypsin is useful for the prevention and/or the treatment of disseminated intravascular coagulation, pancreatitis, severity in pancreatitis and multiple organ failure.

In the specifications of EP-A-588655 and 656349, it is disclosed that certain amidinophenol compounds of the formula (IA) depicted hereinafter have an inhibitory activity on PLA_2 and an inhibitory activity on trypsin and are useful for the prevention and/or the treatment of various inflammatory or allergic diseases, disseminated intravascular coagulation, pancreatitis, severity in pancreatitis and multiple organ failure.

Several amidinophenol derivatives are already known as LTB_4 antagonists. They are disclosed in WO 94/11341, the specification of Japanese Patent Kokai No. 5-239008 and EP-518819. In these applications, it is disclosed that amidinophenyloxy(thio)alkyloxy(thio)benzamide is useful as LTB_4 antagonist.

For example, it is described in the specification of EP-518819 that the compound of the formula (A) :



(A)

wherein R^{1a} is amino which is mono- or disubstituted by a substituent selected from an aliphatic hydrocarbon radical, an araliphatic hydrocarbon radical, an aromatic radical, and a cycloaliphatic hydrocarbon radical or is amino which is disubstituted by a divalent aliphatic hydrocarbon radical; R^{2a} is hydrogen, halogen, trifluoromethyl, an aliphatic hydrocarbon radical, or is hydroxy which is etherified by an aliphatic alcohol, araliphatic alcohol, or aromatic alcohol or which is esterified by an aliphatic or araliphatic carboxylic acid,

R^{3a} is hydrogen or an acyl radical which is derived from an organic carbonic acid, an organic carboxylic acid, a sulfonic acid, or a carbamic acid, X_{1a} and X_{3a}, independently of one another, are oxygen (-O-) or sulphur (-S-),

X_{2a} is a divalent aliphatic hydrocarbon radical which may be interrupted by an aromatic radical,

wherein the phenyl rings of formula (A) may be, independently of one another, further substituted by one or more substituents selected from halogen, trifluoromethyl, an aliphatic hydrocarbon radical, hydroxy, and hydroxy which is etherified by an aliphatic alcohol or which is esterified by an aliphatic or araliphatic carboxylic acid;

wherein aryl moieties in the above definitions may be, independently of one another, further substituted by one or more substituents selected from halogen, trifluoromethyl, an aliphatic hydrocarbon radical, hydroxy, and hydroxy which is etherified by an aliphatic alcohol or which is esterified by an aliphatic or araliphatic carboxylic acid; and

wherein a cycloaliphatic hydrocarbon radical may be substituted by an aliphatic radical,

and pharmaceutically acceptable salts thereof are useful as LTB_4 antagonist.

In the amidinophenyloxy(thio)alkoxy(thio)benzamide compounds represented by EP-518819 as prior art, it can be seen that the existence of -O(or S)-alkylene-O(or S)- (with the proviso that the alkylene may be interrupted by an aromatic group) is essential in the prior art compounds.

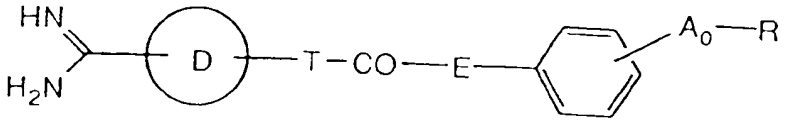
It has now been discovered that compounds in which it is essential that the amidinophenyl is bonded to the phenyl group via an ester or amide group possess useful properties as LTB_4 antagonists, phospholipase A_2 and/or trypsin inhibitors. The amidinophenol derivatives of the invention possess a strong antagonistic activity on LTB_4

That is to say, as mentioned above, compounds of the formula (IA) and processes for the preparation thereof are disclosed in EP-A-588655 and EP-A-656349.

That is to say, the compound of the present invention, of the formula (IB) has an inhibitory activity on phospholipase A_2 and an inhibitory activity on trypsin and it is useful for the prevention and the treatment of various inflammatory, allergic diseases, disseminated intravascular coagulation, pancreatitis, severity in pancreatitis and multiple organ failure.

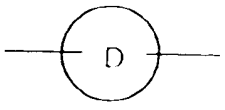
The present invention accordingly provides

1) A new amidinophenol derivative of the formula (IB) :



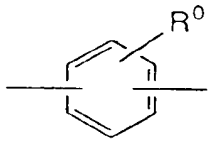
(IB)

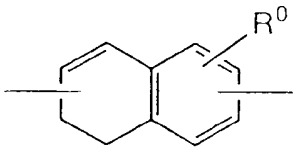
wherein:



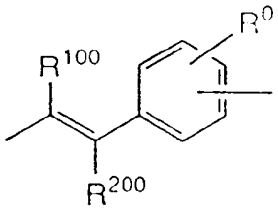
is a group of the formula:

(i)

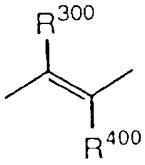


(ii) 

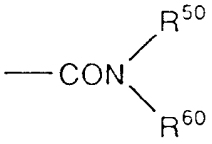
or

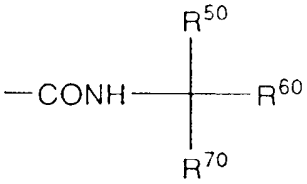
(iii) 

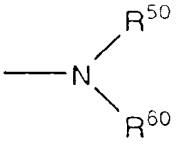
(in which R^0 is hydrogen, or C1-4 alkyl, or C1-4 alkoxy),
T is NH or oxygen,
E is a single bond, or
a group of the formula:

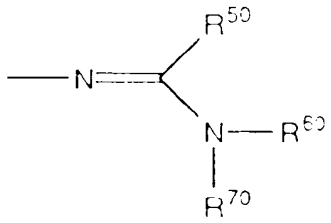


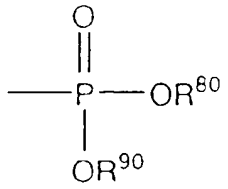
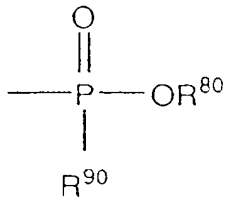
A_0 is a single bond, C1-4 alkylene, -oxy-(C1-4)alkylene-, -thio-(C1-4)alkylene-, C2-8 alkenylene, or C2-8 alkenylene which is substituted by carboxy or by C1-4 alkoxycarbonyl, R^{100}, R^{200}, R^{300} and R^{400} each independently, is hydrogen or C1-4 alkyl,
R is a group of the formula.

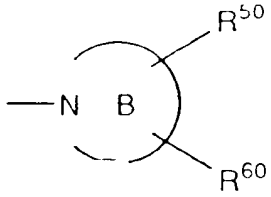
(i) 

(ii) 

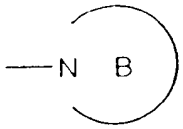
(iii) 

(iv) 

(v)  or  , or

(vi) 

(in which the grouping:



is a 4-10 membered hetero ring containing one or two nitrogen atoms),
R^{50}, R^{60} and R^{70} each independently, is,

(i) hydrogen,

(ii) C1-8 alkyl,

(iii) C2-8 alkenyl

(iv) -$COOR^{110}$ (in which R^{110} is hydrogen or C1-4 alkyl unsubstituted or substituted by phenyl),

(v) -(C1-8 alkylene)-$COOR^{110}$ (in which R^{110} has the same meaning as hereinbefore defined),

(vi) -(C2-8 alkenylene)-$COOR^{110}$ (in which R^{110} has the same meaning as hereinbefore defined),

(vii) C4-7 cycloalkyl,

(viii) -(C1-4 alkylene)-(4-7 membered hetero ring containing one oxygen),

(ix) -(C1-4 alkylene)-(4-7 membered hetero ring containing one nitrogen),

(x) phenyl,

(xi) C1-8 alkyl which is substituted by one or two phenyl,

(xii) -(C1-4 alkylene)-O-benzoyl,

(xiii) -(C1-4 alkylene)-CONH-(C1-4 alkylene)-$NR^{120}R^{130}$,

(xiv) -(C1-4 alkylene)-COO-(C1-4 alkylene)-$NR^{120}R^{130}$,

(xv) -(C1-4 alkylene)-COO-amidinophenyl,

(xvi) -(C1-4 alkylene)-CONH-(C1-4 alkyl which is substituted by one or two -$COOR^{110}$) (in which R^{110} has the same meaning as hereinbefore defined),

(xvii) -(C1-4 alkylene)-$CONR^{120}R^{130}$, or

(xviii) (C1-4)alkoxy(C1-4)alkyl,

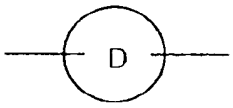
R^{80} and R^{90} each independently, is C1-4 alkyl or -(C1-4 alkylene)-phenyl, R^{120} and R^{130} each independently, is hydrogen, C1-4 alkyl, or C2-8 alkenyl, with the provisos that:

(1) R^{50} and R^{60} in the formulae (i) and (iii), and R^{50}, R^{60} a in the formulae (ii) and (iv), do not represent hydrogen ; same time,

(2) when at least one substituent in R^{50}, R^{60}, R^{70} and A_0 represent substituent containing -COO-t-Bu, the other groups do not represent groups containing carboxy,

(3) R^{120} and R^{130} do not represent hydrogen at the same time,

(4) when
T is oxygen,
the grouping:



is the formula (i) as hereinbefore described,
E is a single bond,
A_0 is a single bond, C1-4 alkylene or vinylene which is optionally substituted by one or two C1-4 alkyl, and R is the formula (i) as hereinbefore described,
then at least one group in R^{50}, R^{60} and R^{70} is

(viii) -(C1-4 alkylene)-(4-7 membered hetero ring containing one oxygen),

(ix) -(C1-4 alkylene)-(4-7 membered hetero ring containing one nitrogen),

(x) phenyl,

(xi) C1-8 alkyl which is substituted by one or two phenyl,

(xii) -(C1-4 alkylene)-benzoyl,

(xiii) -(C1-4 alkylene)-CONH-(C1-4 alkylene)-$NR^{120}R^{130}$,

(xiv) -(C1-4 alkylene)-COO-(C1-4 alkylene)-$NR^{120}R^{130}$,

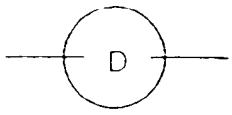
(xv) -(C1-4 alkylene)-COO-;amidinophenyl,

(xvi) -(C1-4 alkylene)-CONH-(C1-4 alkyl which is substituted by one or two -$COOR^{110}$) (in which R^{110} has the same meaning as hereinbefore defined),

(xvii) -(C1-4 alkylene)-$CONR^{120}R^{130}$, or

(xviii) -(C1-4)alkoxy(C1-4)alkyl;

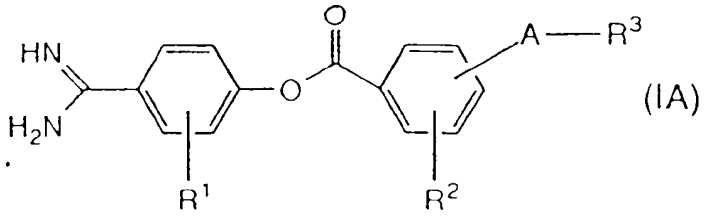
(5) when
T is oxygen,
the grouping



is the formula (i) as hereinbefore defined,
E is a single bond,
A_0 is a single bond, C1-4 alkylene or vinylene which may be optionally substituted by one or two C1-4 alkyl, and R is the formula (ii) as hereinbefore defined,
then R^{50}, R^{60} and R^{70} do not represent hydrogen,
and non-toxic salts thereof or non-toxic acid addition salts thereof.

The compounds of the invention may form hydrates: it is to be understood that such hydrates form part of the present invention and that references to the compounds in this specification including the accompanying claims are to be understood as embracing the hydrates.

The invention also provides a compound of the formula (IA):



(IA)

wherein R^1 and R^2 each independently, is:

(i) hydrogen, or

(ii) $-COOR^4$ (in which R^4 is C1-3 alkyl);

A is

(i) a single bond,

(ii) C1-4 alkylene, or

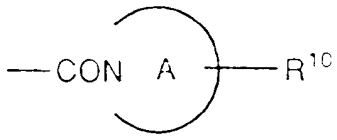
(iii) $-C(R^5)=C(R^6)-$ (in which R^5 and R^6 each independently, is hydrogen or C1-4 alkyl);

R^3 is

(i) $-CON(R^7)R^8$,

(ii) $-CONR^9-CH(R^7)R^8$, or

(iii)



(wherein R^7 and R^8 each independently, is

(1) hydrogen,

(2) phenyl,

(3) -(C1-4 alkylene)-phenyl,

(4) -(C1-4 alkylene)-phenyl which is substituted by one or two $-R^{11}-COOR^{12}$ (in which R^{11} is a single bond or C1-8 alkylene, and R^{12} is hydrogen or C1-4 alkyl),

(5) C1-5 alkyl,

(6) C2-10 alkenyl containing one to three double bonds,

(7) $-R^{11a}-COOR^{12}$ (in which R^{11a} is

(a) a single bond,

(b) C1-8 alkylene,

(c) C2-8 alkenylene, or

(d) C4-8 alkenylene in which one or two carbon atoms in the main chain are replaced by sulfur, and R^{12} has the same meaning as hereinbefore defined), or

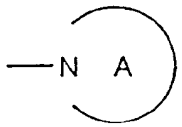
(8) C3-7 cycloalkyl;

R^9 is

(1) hydrogen,

(2) $-R^{11}-COOR^{12}$ (in which the various symbols have the same meanings as hereinbefore defined), or

(3) C2-6 alkoxyalkyl;
the grouping:



is a 4-7 membered mono hetero ring contain one or two nitrogen;

R^{10} is

(1) hydrogen, or

(2) -(C1-4 alkylene)-phenyl,
with the proviso that:

(1) both R^7 and R^8 do not represent hydrogen at the same time,

(2) when at least one group in R^7, R^8, and R^9 represent the group containing -COO-t-Bu, the other groups do not represent the groups containing carboxy;

non-toxic salts thereof and non-toxic acid-addition salts thereof, for use in the manufacture of a medicament for the treatment of a condition which can be ameliorated by the administration of an LTB_4 antagonist.

The invention also provides a compound of formula (IB) or a non-toxic salt thereof or a non-toxic acid addition salt thereof for use in the manufacture of a medicament for the treatment of a condition which can be ameliorated by the administration of a phospholipase A_2 or trypsin inhibitor.

Throughout the specification, it will be understood by those skilled in the art, that all isomers are included in the present invention. For example, the alkyl, alkoxy, alkylene, alkenylene and alkynylene groups include straight-chain and also branched-chain ones, and the double bonds in the alkenylene group include E, Z and EZ mixtures. Accordingly, all isomers produced by the existence of asymmetric carbon atoms are included in the present invention when branched-chain alkyl, alkoxy, alkylene, alkenylene and alkynylene, are present. Explanation of various symbols in the formula (IB) is shown below.

The C1-3 alkyl group means methyl, ethyl, propyl and the isomers thereof. C1-4 alkyl group means butyl in addition to the groups above mentioned, and the isomers thereof. C1-5 alkyl group means pentyl in addition to the groups above mentioned, and the isomers thereof.

C1-4 alkylene group means methylene, ethylene, trimethylene, tetramethylene and the isomers thereof. C1-8 alkylene group means pentamethylene, hexamethylene, heptamethylene, octamethylene in addition to the groups above mentioned, and the isomers thereof. C2-6 alkoxyalkyl group means ethyl, butyl, propyl, pentyl, hexyl and the straight or branched-chain isomers thereof, which are interrupted by oxygen except at their end. Representative of such alkoxyalkyl groups are: $-CH_2-O-CH_3$, $-CH_2-O-CH_2-CH_3$, $-(CH_2)_2-O-CH_3$, $-CH_2-O-(CH_2)_2-CH_3$, $-(CH_2)_2-O-CH_2-CH_3$, $-(CH_2)_3-O-CH_3$, $-CH_2-O-(CH_2)_3-CH_3$, $-(CH_2)_2-O-(CH_2)_2-CH_3$, $-(CH_2)_3-O-CH_2-CH_3$, $-(CH_2)_4-O-CH_3$, $-CH_2-O-(CH_2)_4-CH_3$, $-(CH_2)_2-O-(CH_2)_3-CH_3$, $-(CH_2)_3-O-(CH_2)_2-CH_3$, $-(CH_2)_4-O-CH_2-CH_3$, $-(CH_2)_5-O-CH_3$.

C4-8 alkenylene group means tetramethylene, pentamethylene, hexamethylene, heptamethylene, octamethylene in which a $-CH_2-CH_2-$ grouping (which is not at either end of the group) is replaced by a double bond.

C2-8 alkenylene group containing one to three double bonds means ethylene, trimethylene, tetramethylene, pentamethylene, hexamethylene, heptamethylene or octamethylene in which one to three groupings $-CH_2-CH_2-$ (except those at each end of the group) are replaced by double bonds.

C3-7 cycloalkyl group means cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl or cycloheptyl.

The 4-7 membered hetero ring containing one or two nitrogen means, for example, pyrrolyl, pyrrolidinyl, imidazolyl, imidazolidinyl, pyridinyl, piperidinyl, pyrazinyl, piperazinyl or pyrimidinyl. Explanation of various symbols in the formula (IB), is shown below.

In the formula (IB), C1-4 alkyl represented by R^0, R^{100}, R^{200}, R^{300}, R^{400}, R^{50}, R^{60}, R^{70}, R^{80}, R^{90}, R^{120} and R^{130}, and that in R^0, R^{100}, R^{200}, R^{300}, R^{400}, R^{50}, R^{60}, R^{70}, R^{80}, R^{90}, R^{120} and R^{130}, means methyl, ethyl, propyl, butyl and the isomers thereof.

In the formula (IB), C1-4 alkyl represented by R^0 and A_0, and that in R^0 and A_0 means methoxy, ethoxy, propoxy, butoxy and the isomers thereof.

In the formula (IB), C1-4 alkylene represented by A_0, and that in A_0, means methylene, ethylene, trimethylene, tetramethylene and the isomers thereof.

In the formula (IB), C2-8 alkenylene represented by A_0, and that in A_0, means ethylene, trimethylene, tetramethylene, pentamethylene, hexamethylene, heptamethylene, octamethylene and the isomers thereof, having one, two or three double bonds.

In the formula(IB), C1-8 alkyl represented by R^{50}, R^{60} and R^{70}, and that in R^{50}, R^{60} and R^{70}, means methyl, ethyl, propyl, butyl, pentyl, hexyl, heptyl, octyl and the isomers thereof.

In the formula (IB), C2-8 alkenyl represented by R^{50}, R^{60} and R^{70}, and that in R^{50}, R^{60} and R^{70}, mean methyl, ethyl, propyl, butyl, pentyl, hexyl, heptyl, octyl and the isomers thereof, having one, two or three double bonds.

In the formula (IB), 4-7 cycloalkyl represented by R^{50}, R^{60} and R^{70}, and that in R^{50}, R^{60}, and R^{70}, mean cyclobutyl, cyclopentyl, cyclohexyl and cycloheptyl.

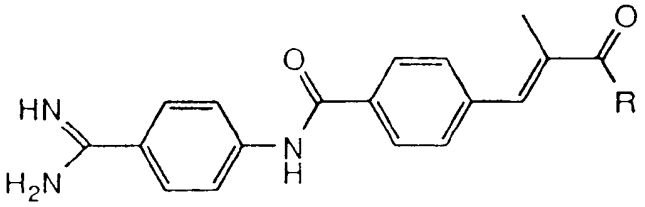
In the formula (IB), examples of the 4-7 membered hetero ring containing one oxygen (which may be partially or fully saturated) represented by R^{50}, R^{60}, and R^{70}, and that in R^{50}, R^{60}, and R^{70}, are furyl, pyranyl, dihydrofuryl, dihydropyranyl, tetrahydrofuryl and tetrahydropyranyl.

In the formula (IB), examples of the 4-7 membered hetero ring containing one nitrogen (which may be partially or fully saturated) represented by R^{50}, R^{60}, and R^{70}, and that in R^{50}, R^{60}, and R^{70}, are pyrrolyl, pyridinyl, piperidinyl, pyrrolinyl, pyrrolidinyl and dihydropyridinyl.

In the formula (IB), when R is the formula represented by (vi), examples of the 4-10 membered hetero ring containing one or two nitrogen, (which may be partially or fully saturated) are pyrrolyl, pyridinyl, pyrrolinyl, pyrrolidinyl, dihydropyridinyl, imidazolyl, piperidinyl, imidazolinyl, imidazolidinyl, pyrimidinyl, pyridazinyl, pyrazinyl, indolyl and tetrahydroindolyl.

Preferred compounds of the present invention of the formula (IB) are those described in the Examples and the following compounds.

Table 1



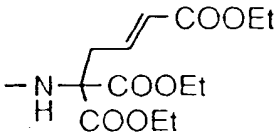
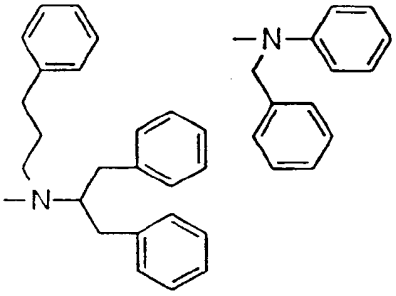
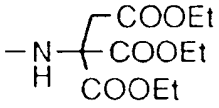
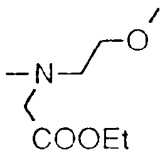
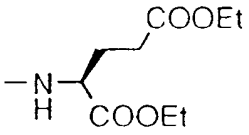
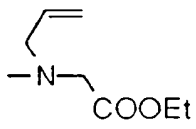
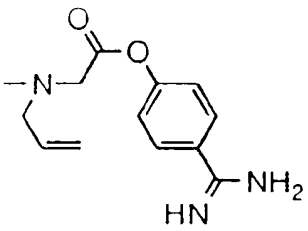
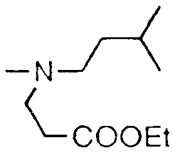
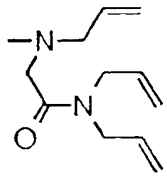
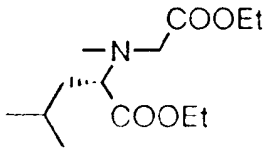
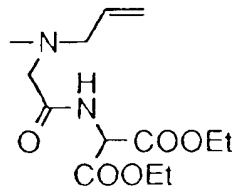
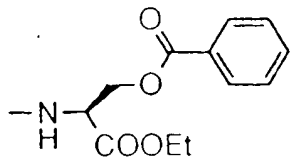
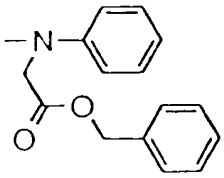
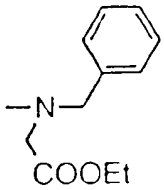
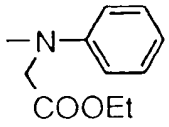
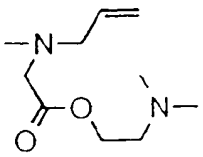
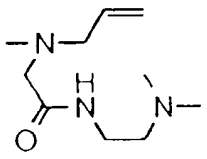
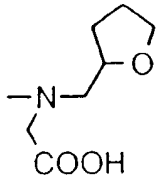
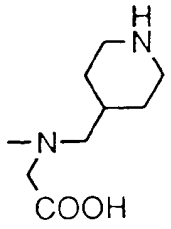
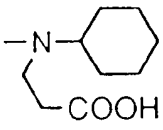
Preferable groups as R	
	
	
	
	
	
	
	
	
	

Table 1 continued

Preferable groups as R	
	
	
	

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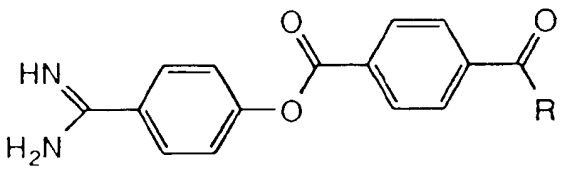


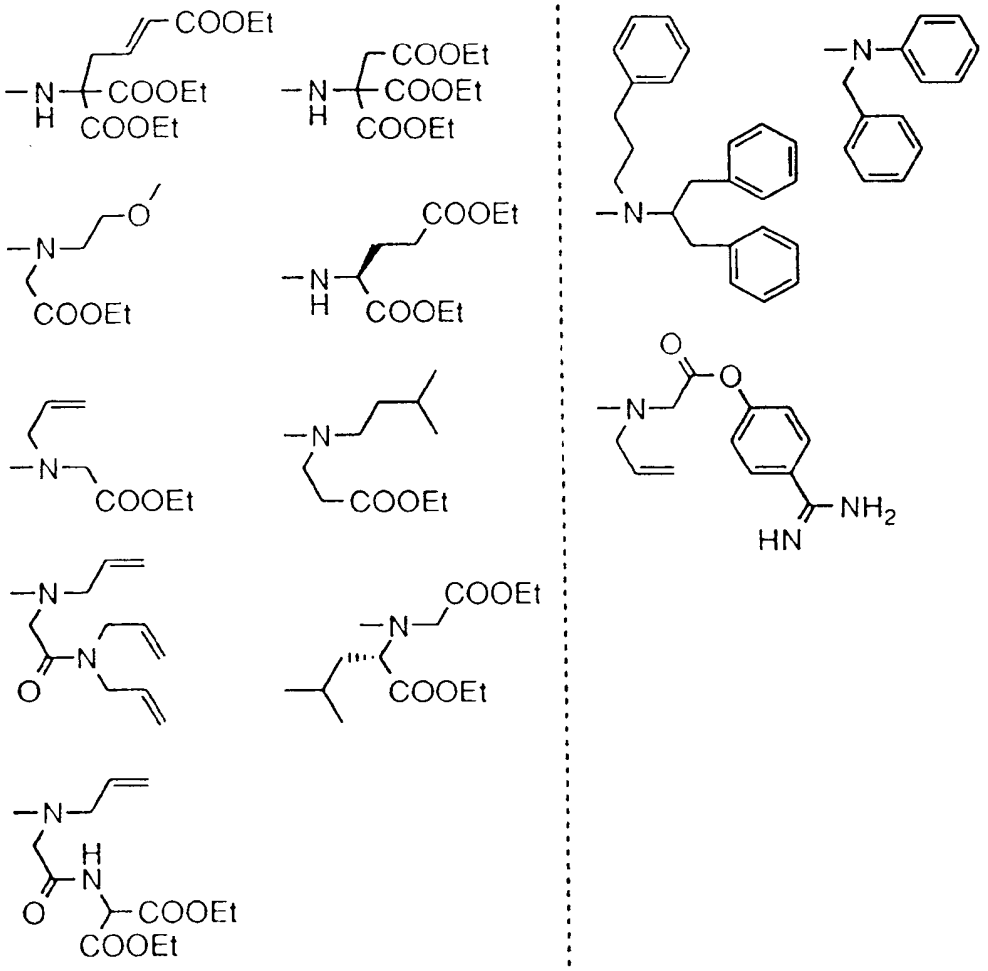
Preferable groups as R


Table 2 continued

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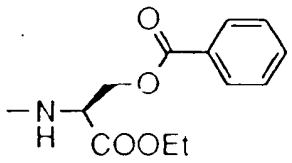	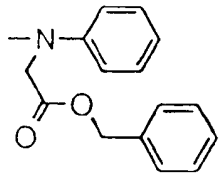
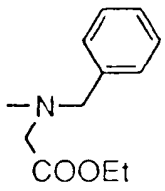	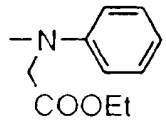
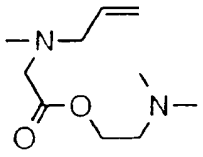	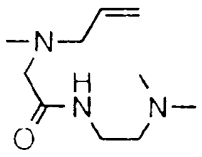

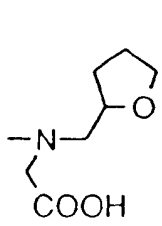
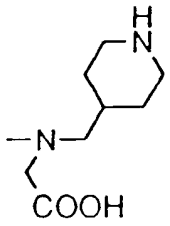
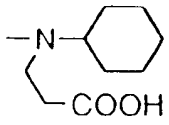

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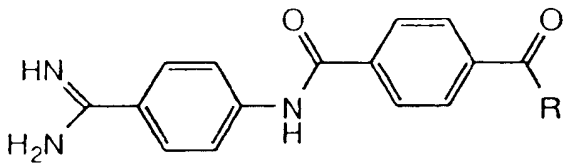


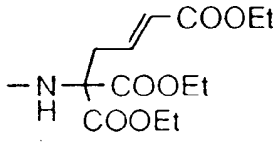
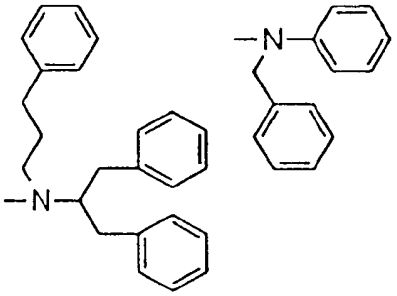
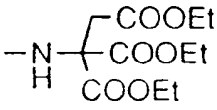
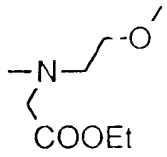
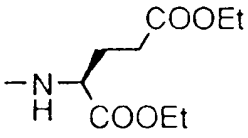
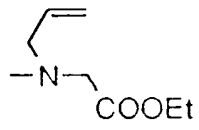
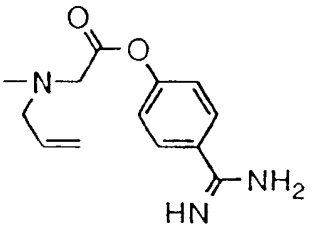
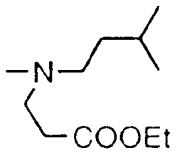
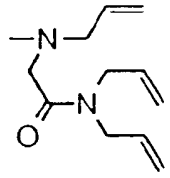
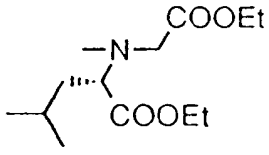
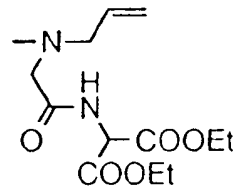
Preferable groups as R	
	
	
	
	
	
	
	
	
	

Table 3 continued

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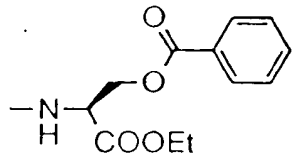	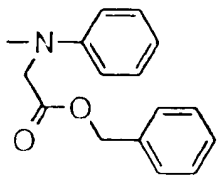	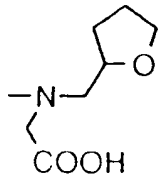	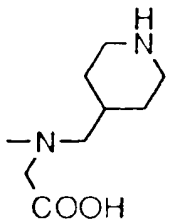
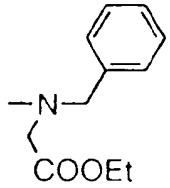	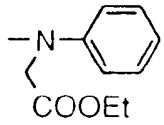	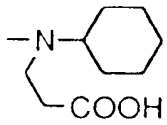	
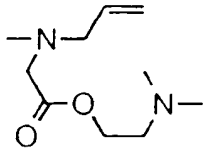	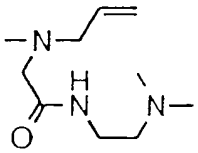		

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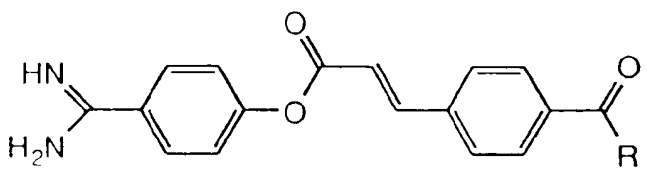
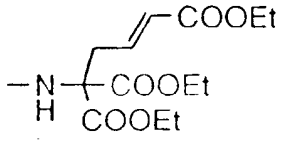
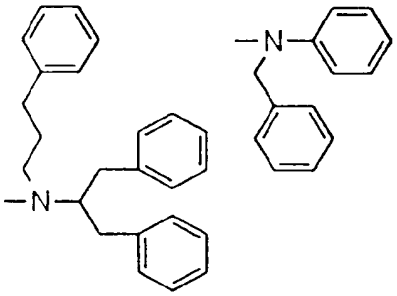
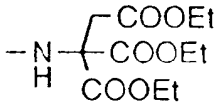
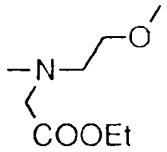
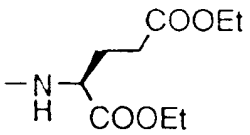
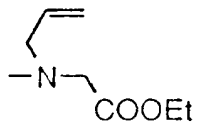
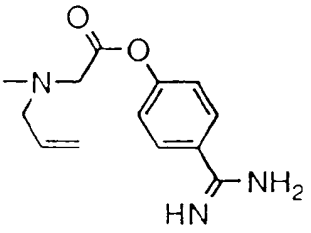
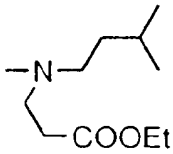
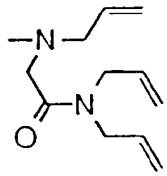
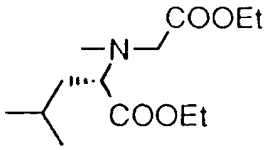
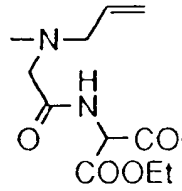


Preferable groups as R	
	
	
	
	
	
	
	
	
	

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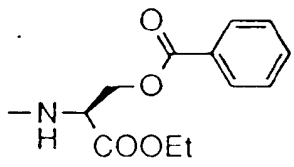	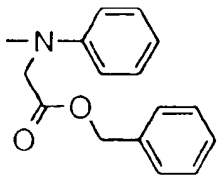
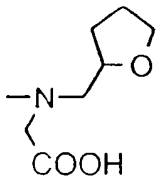	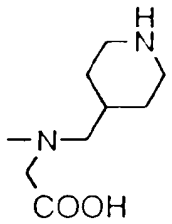
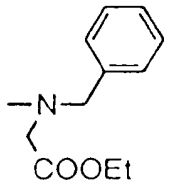	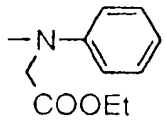
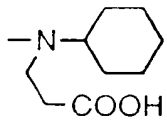	
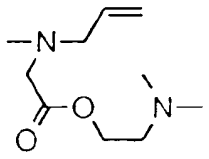	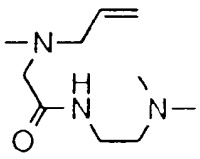

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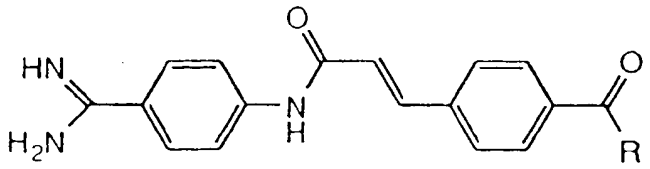


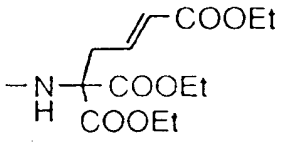
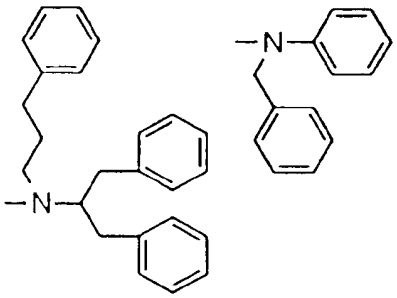
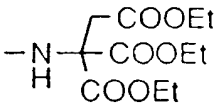
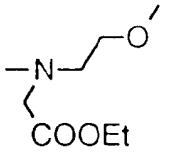
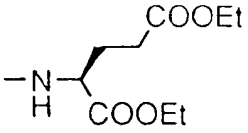
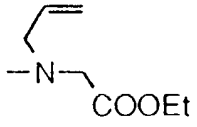
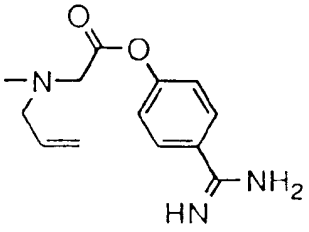
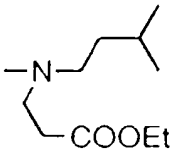
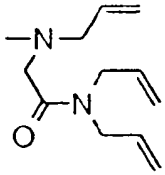
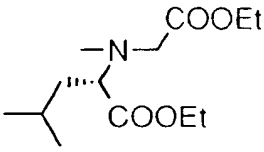
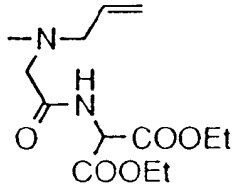
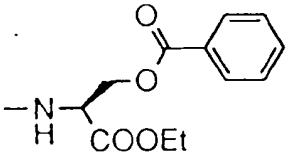
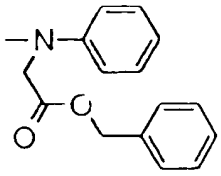
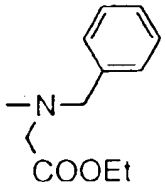
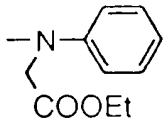
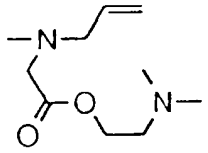
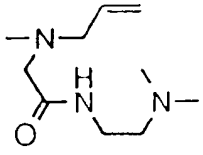
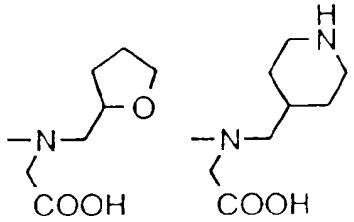
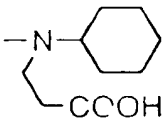
Preferable groups as R	
	
	
	
	
	
	
	
	
	

Table 5 continued

Preferable groups as R	
	
	
	





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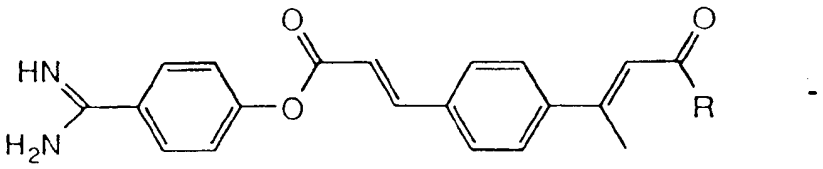


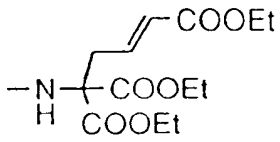
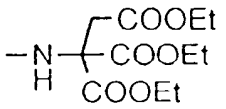
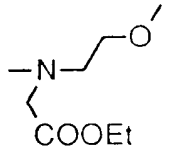
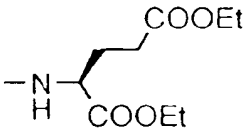
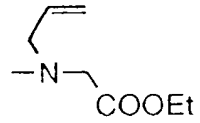
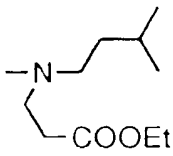
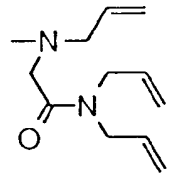
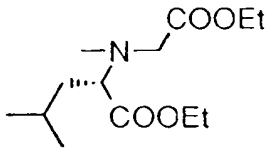
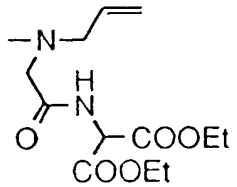
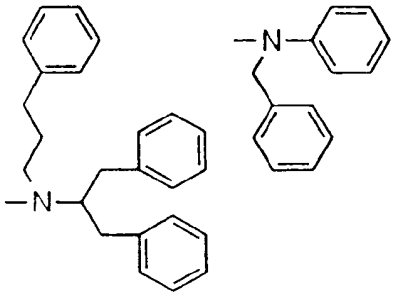
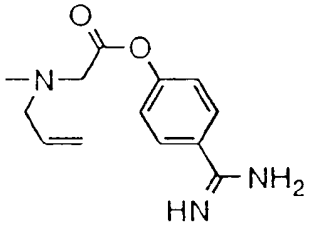
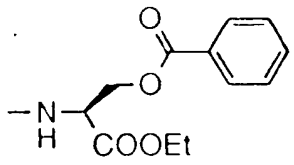
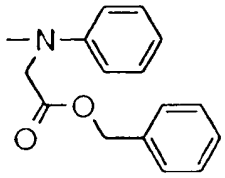
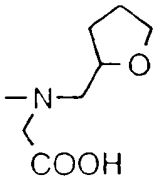
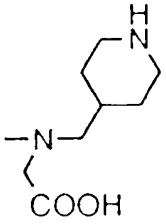
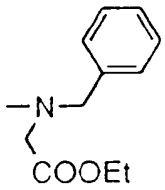
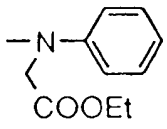
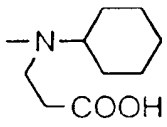
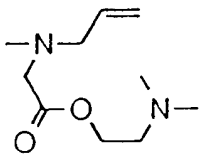
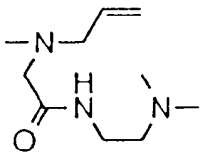
Preferable groups as R
          

Table 6 continued

Preferable groups as R	
	
	
	
	
	

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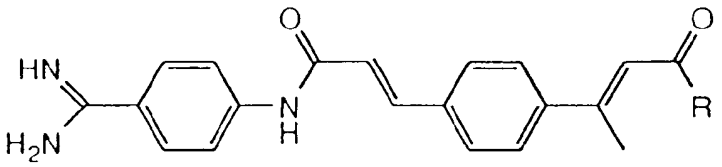


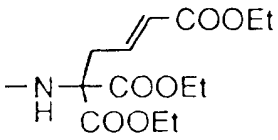
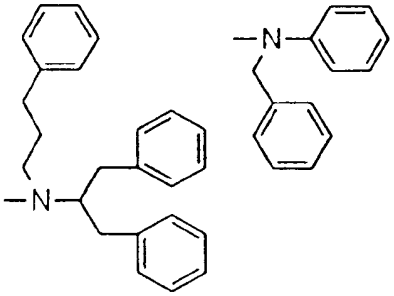
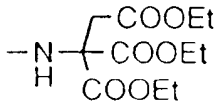
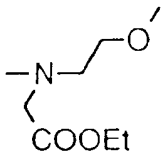
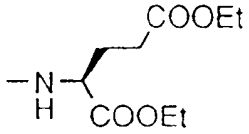
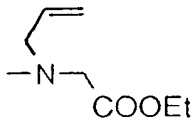
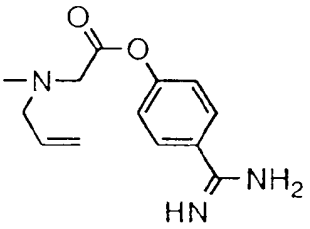
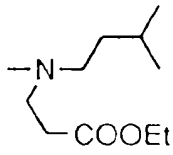
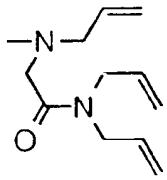
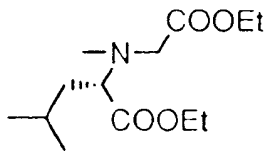
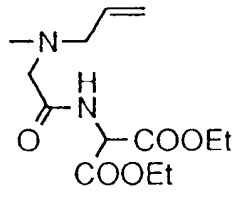
Preferable groups as R	
	
	
	
	
	
	
	
	
	

Table 7 continued

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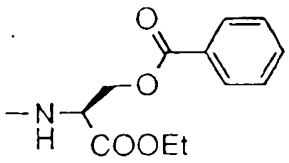	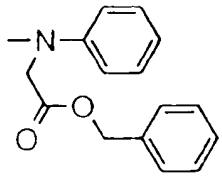
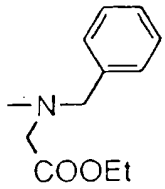	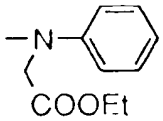
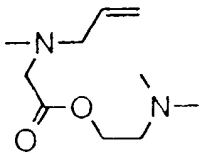	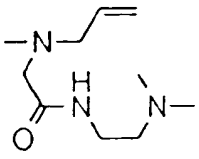

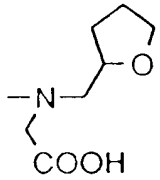
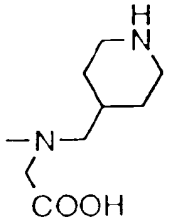
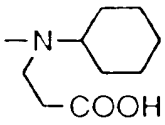

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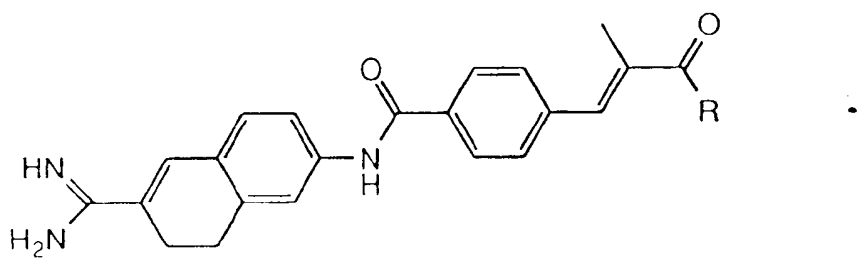
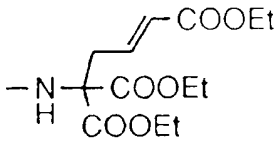
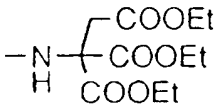
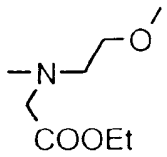
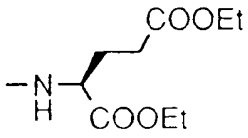
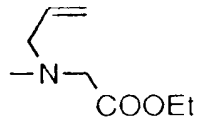
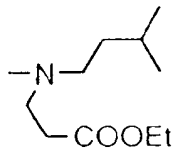
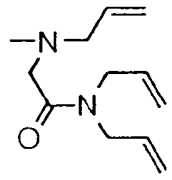
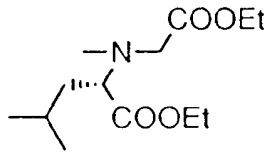
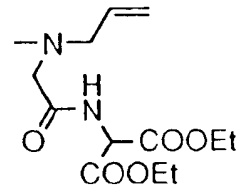


Preferable groups as R	
	
	
	
	
	

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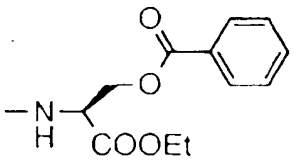	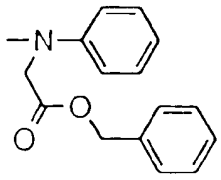
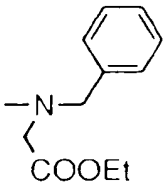	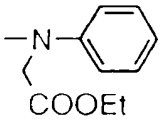
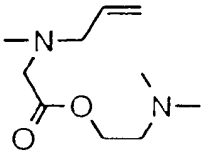	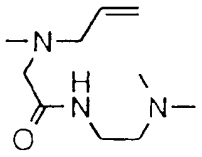

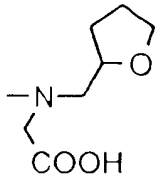

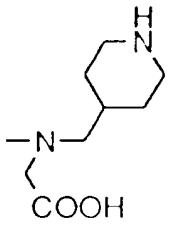

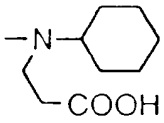

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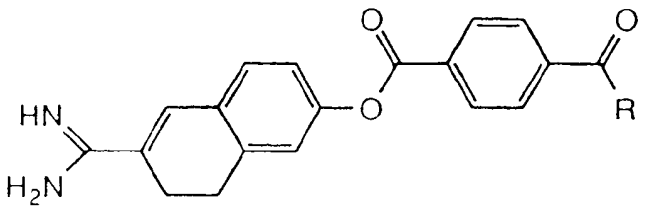


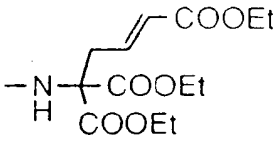
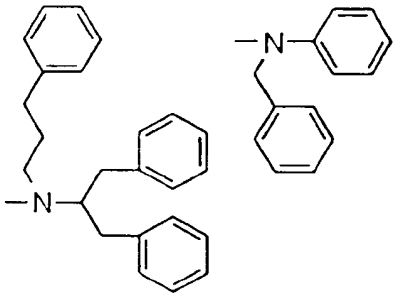
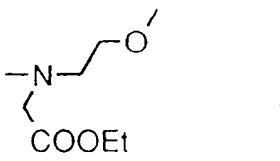
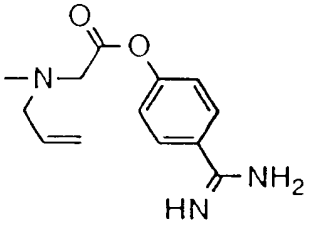
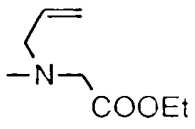
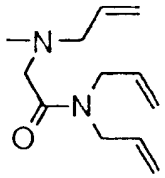
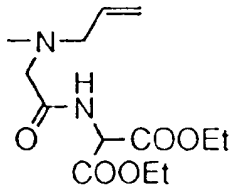
Preferable groups as R	
	
	
	
	
	

Table 9 continued

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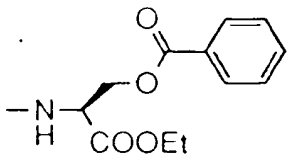	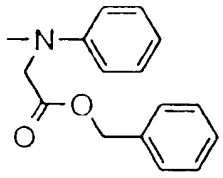
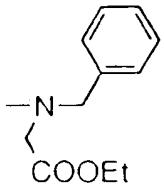	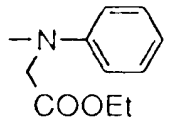
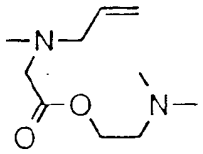	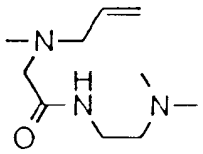

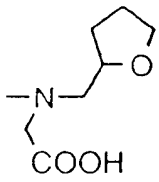

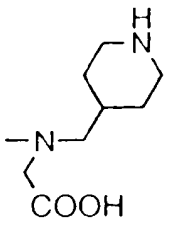

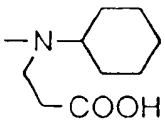

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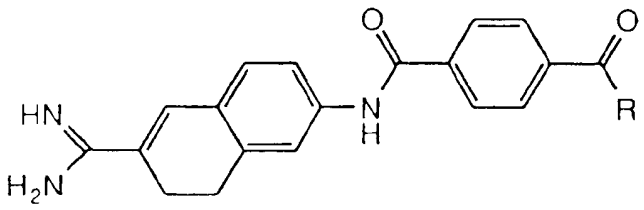


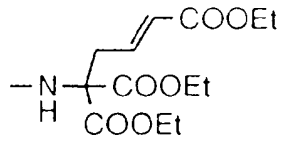
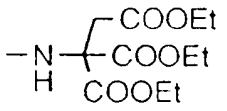
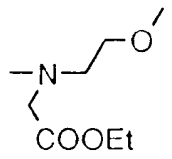
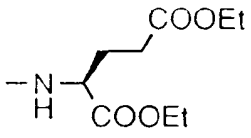
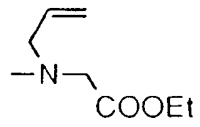
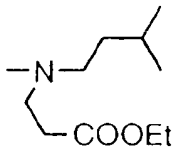
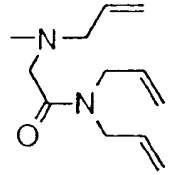
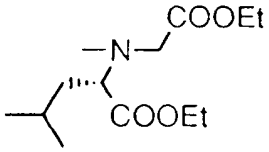
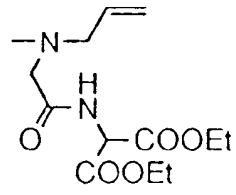
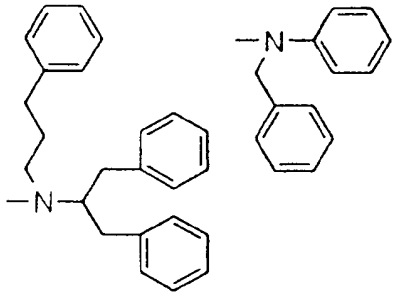
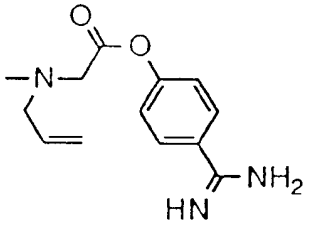
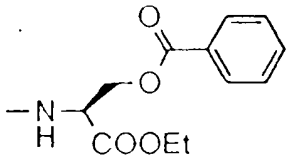
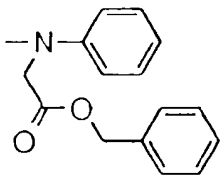
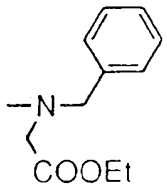
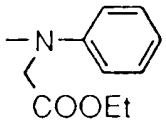
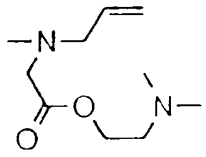
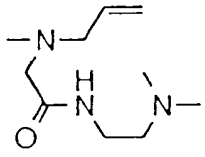
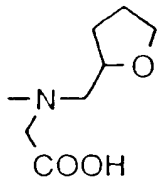
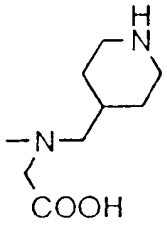
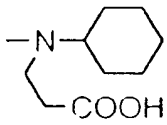
Preferable groups as R
          

Table 10 continued

Preferable groups as R	
	
	
	







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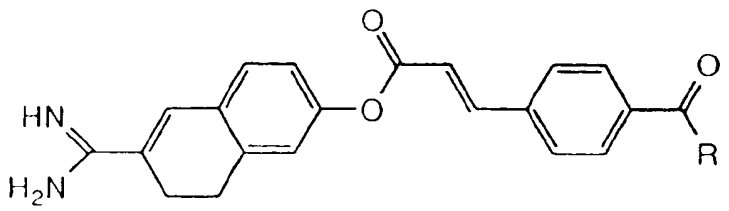


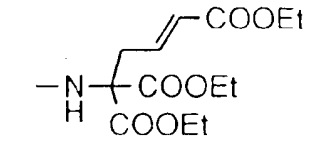
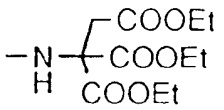
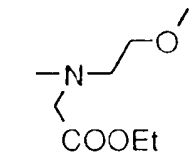
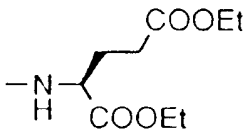
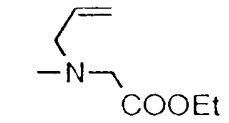
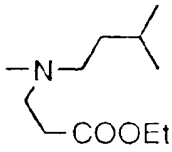
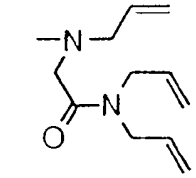
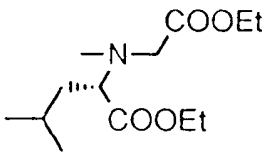
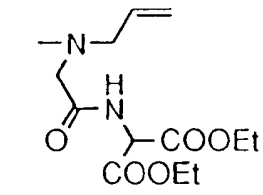
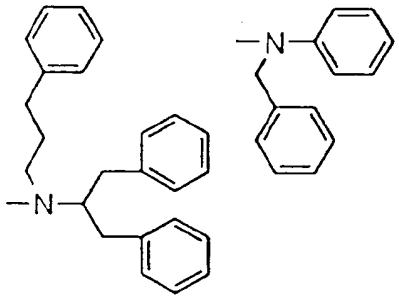
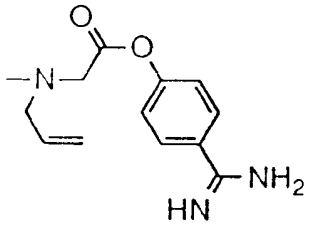
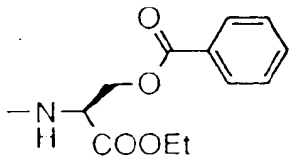
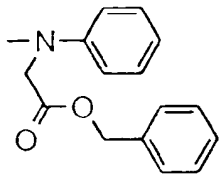
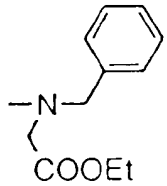
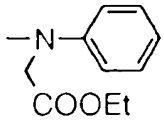
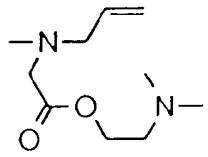
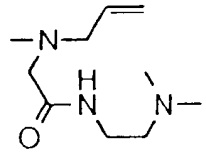
Preferable groups as R
          

Table 11 continued

Preferable groups as R	
	
	
	

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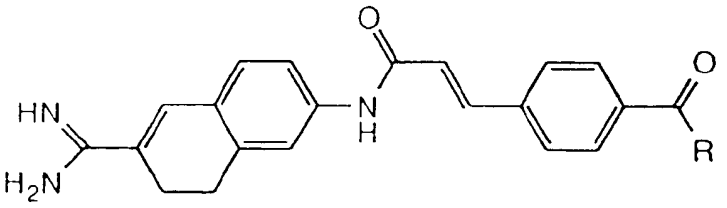


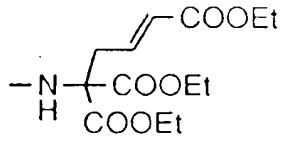
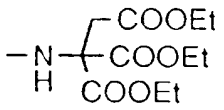
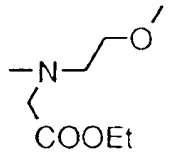
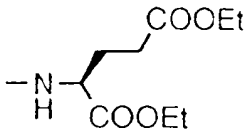
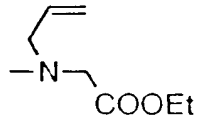
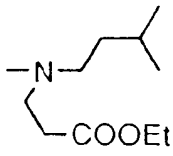
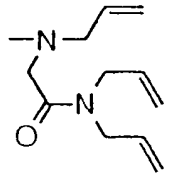
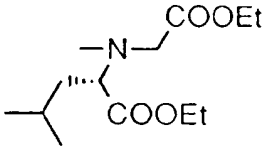
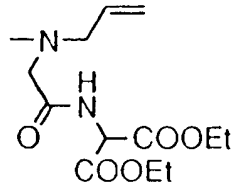
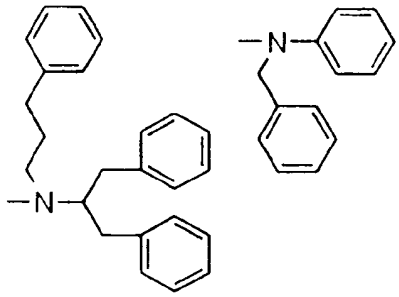
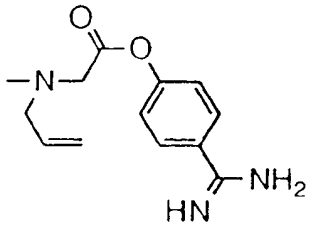
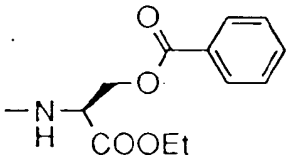
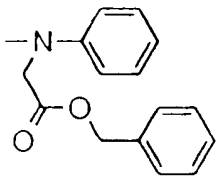
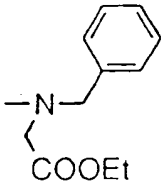
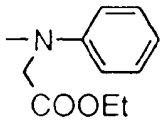
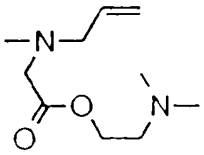
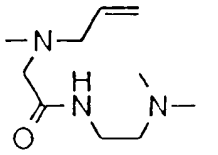
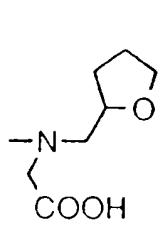
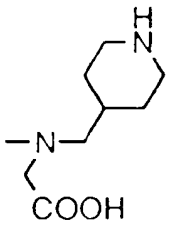
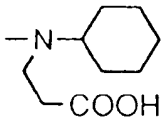
Preferable groups as R
          

Table 12 continued

Preferable groups as R	
	
	
	







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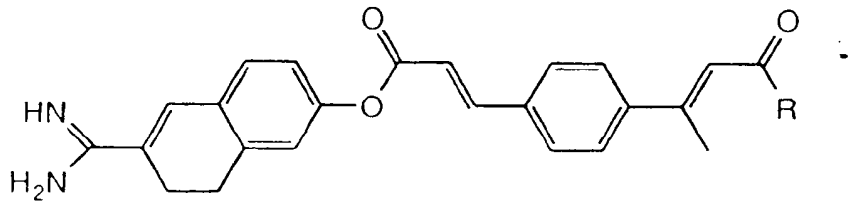


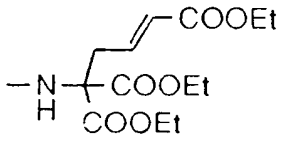
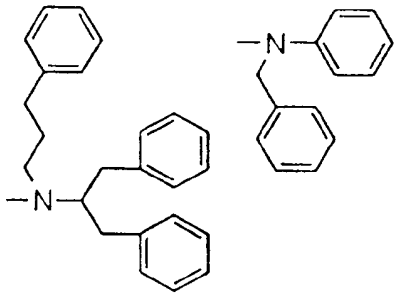
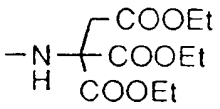
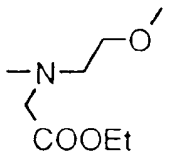
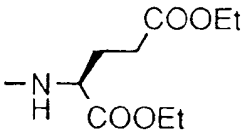
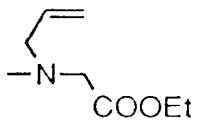
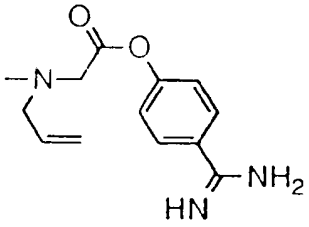
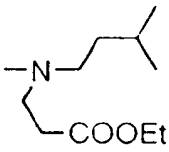
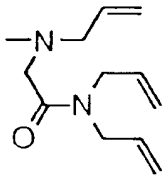
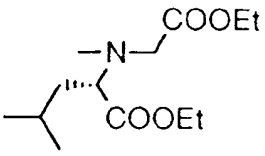
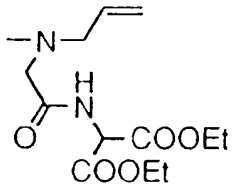
Preferable groups as R	
	
	
	
	
	
	
	
	
	

Table 13 continued

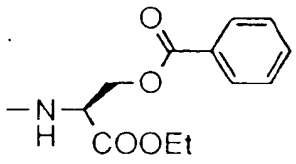
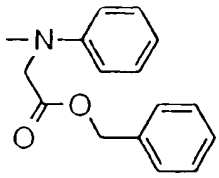
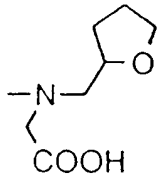
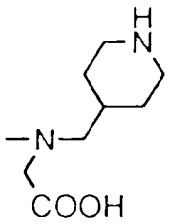
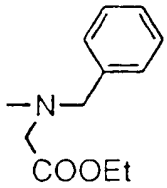
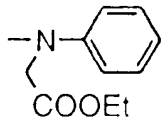
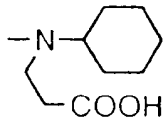
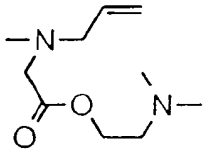
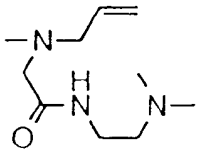
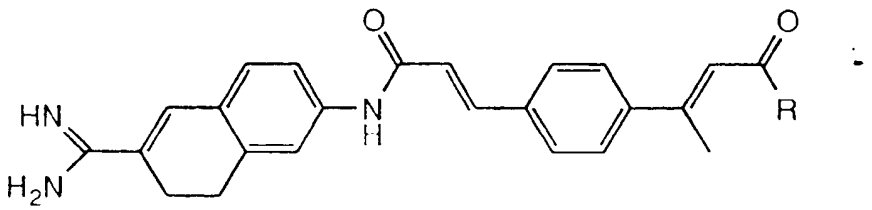
Preferable groups as R			
			
			
			

Table 14



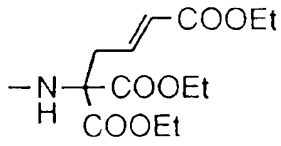
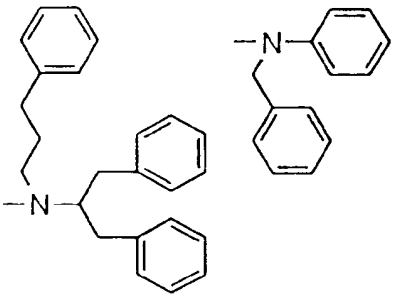
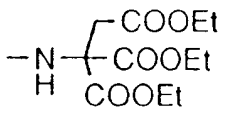
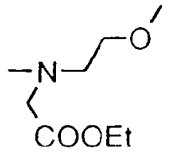
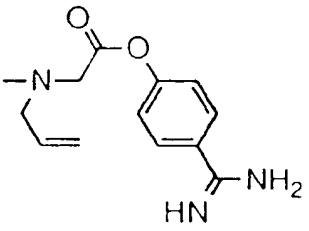
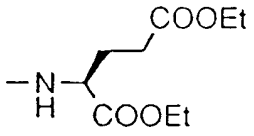
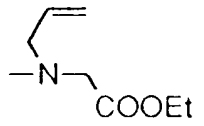
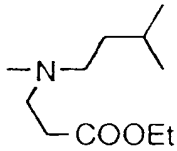
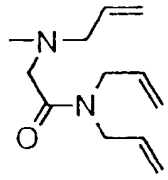
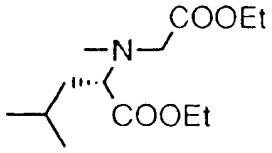
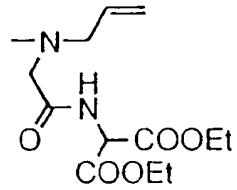
Preferable groups as R	
	
	
	
	
	
	
	
	
	

Table 14 continued

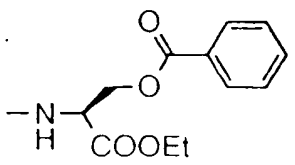
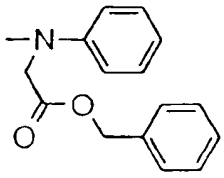
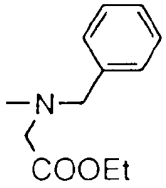
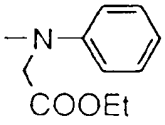
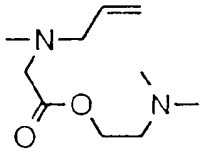
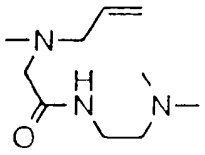
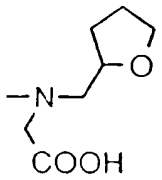
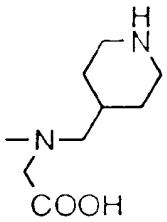
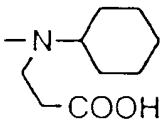
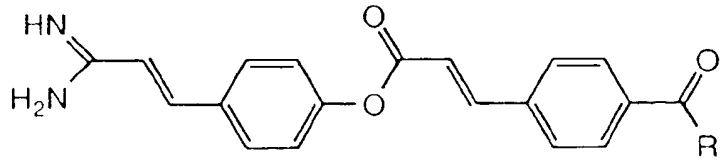
Preferable groups as R	
     	  

Table 15



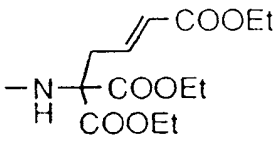
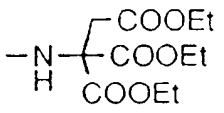
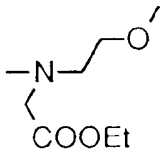
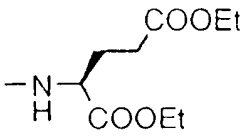
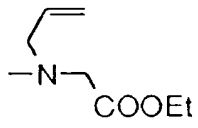
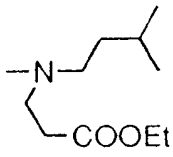
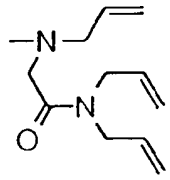
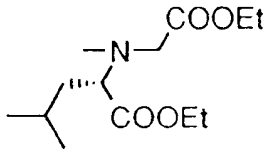
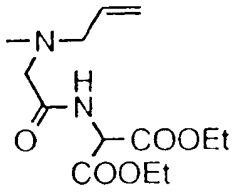
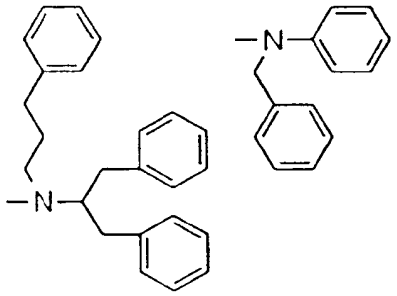
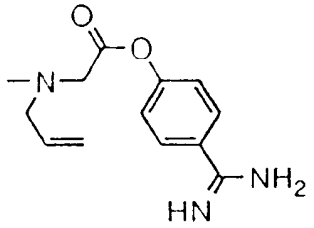
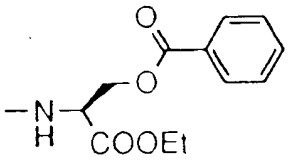
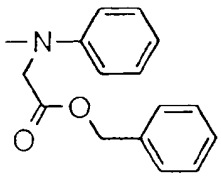
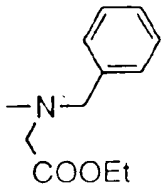
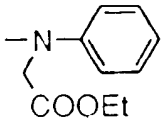
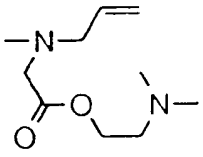
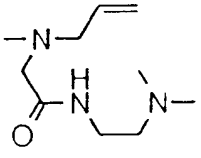
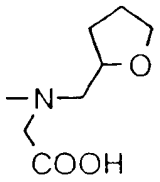
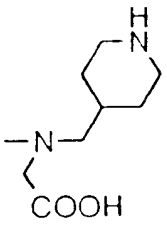
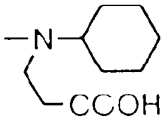
Preferable groups as R
          

Table 15 continued

Preferable groups as R	
	
	
	







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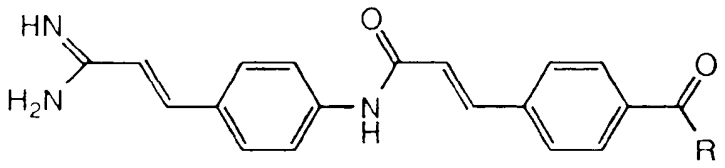


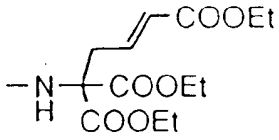
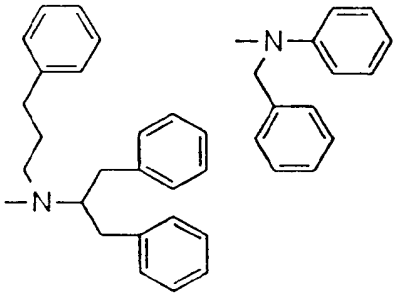
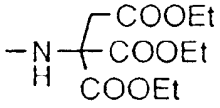
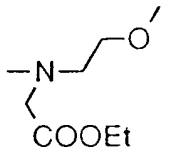
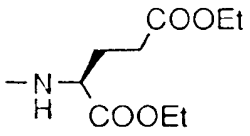
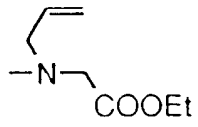
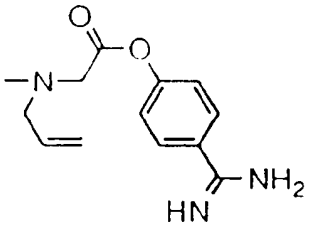
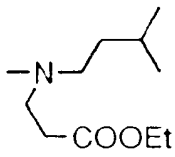
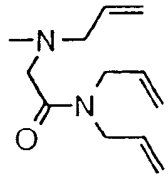
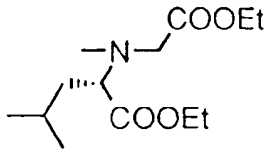
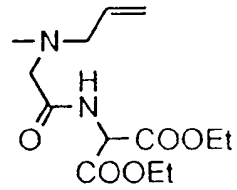
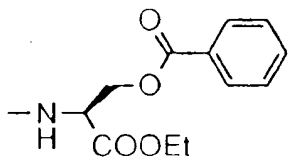
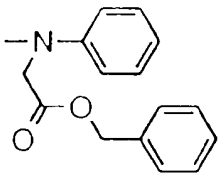
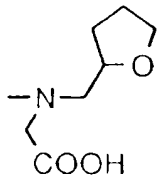
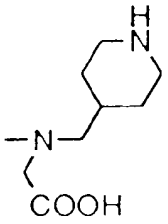
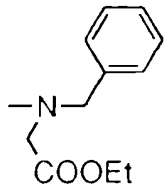
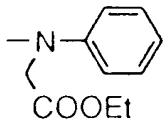
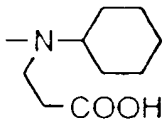
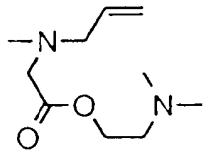
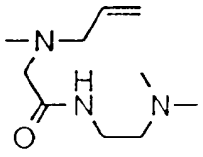
Preferable groups as R	
	
	
	
	
	
	
	
	
	

Table 16 continued

Preferable groups as R			
			
			
			

Pharmaceutical compositions of the present invention can be prepared using one active ingredient or two or more active ingredients.

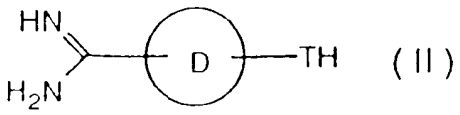
The compounds of the formula (IA) and (IB) , of the present invention may be converted into the corresponding salts and acid-addition salts by known methods. Nontoxic and water-soluble salts are preferred.

Suitable salts include the salts of alkali metals (sodium, potassium etc), alkaline-earth metal (calcium. magnesium etc.), ammonium salts, salts of pharmacologically acceptable organic amines (tetramethyl ammonium, triethylamine, methylamine, dimethylamine, cyclopentylamine, benzylamine, phenetylamine, piperidine, monoethanolamine, diethanolamine, tris (hydroxymethyl)aminomethane, lysine, arginine, N-methyl-D-gulcane etc).

Suitable acid-addition salts include the salts with inorganic acids such as hydrochloric acid, and the salts with organic acids such as acetic acid, trifluoroacetic acid, lactic acid, tartaric acid, oxalic acid, fumaric acid, maleic acid, citric acid, benzoic acid, methanesulfonic acid, ethanesulfonic acid, benzenesulfonic acid, toluenesulfonic acid, isethionic acid, glucuronic acid and gluconic acid. Preferred salts include the salts with acids such as hydrochloric acid, methanesulfonic, acetic acid and trifluoroacetic acid.

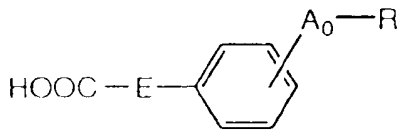
The compounds of the present invention, of the formula (IA), may be prepared by methods known per se, as hereinbefore defined (see the specification of EP-A-588655 and EP-A-656349).

The compounds of the present invention, of the formula (IB) may be prepared by the reaction to form an ester or amide bond of a compound of the formula (II):



(II)

(wherein the various symbols have the same meanings as hereinbefore defined) with a compound of the formula.



(wherein the various symbols have the same meanings as hereinbefore defined). The esterification and the reaction to form an amide are known and can be carried out by known methods for example.

(1) using an acid halide,

(2) using a mixed acid anhydride or

(3) using a condensing agent

Esterification can be carried out, for example, as follows:

(1) the method using an acid halide may be carried out, for example, by reacting a carboxylic acid with an acid halide (e. g., oxalyl chloride, thionyl chloride etc.) in an inert organic solvent (e.g., chloroform, methylene chloride, diethyl ether, tetrahydrofuran etc.) or without a solvent at from -20°C to the reflux temperature of the solvent, and then by reacting the acid halide obtained with a corresponding alcohol in the presence of a tertiary amine (e.g., pyridine, triethylamine, diethylaniline, diethylaminopyridine etc.) in an inert organic solvent (e. g., chloroform, methylene chloride, diethyl ether, tetrahydrofuran etc.) at a temperature of from 0°C to 40°C,

(2) the method using a mixed acid anhydride may be carried out, for example, by reacting a carboxylic acid and an acid halide (e. g., pivaloyl chloride, tosyl chloride, mesyl chloride etc.) or an acid derivative (e. g., ethyl chloroformate, isobutyl chloroformate etc.) in the presence of a tertiary amine (e.g. pyridine, triethylamine, dimethylaniline, dimethylaminopyridine etc.) in an inert organic solvent (e. g., chloroform, methylene chloride, diethyl ether, tetrahydrofuran etc.) or without a solvent at a temperature of from 0°C to 40°C, and then by reacting the mixture of acid anhydride obtained with a corresponding alcohol in an inert organic solvent (e. g., chloroform, methylene chloride, diethyl ether, tetrahydrofuran etc.), at a temperature of from 0°C to 40°C,

(3) the method using a condensing agent (e. g., 1,3-dicyclohexylcarbodiimide (DCC), 1-ethyl-3-[(dimethylamino) propyl] carbodiimide(EDC), 2-chloro-1-methypyridinium iodide etc.) may be carried out, for example, by reacting a carboxylic acid with a corresponding alcohol using a condensing agent in the presence or absence of a tertiary amine (e.g. pyridine, triethylamine, dimethylaniline, dimethylaminopyridine etc.) in an inert organic solvent (e. g., chloroform, methylene chloride, dimethyl formamide, diethyl ether etc.) or without a solvent at a temperature of from 0°C to 40°C.

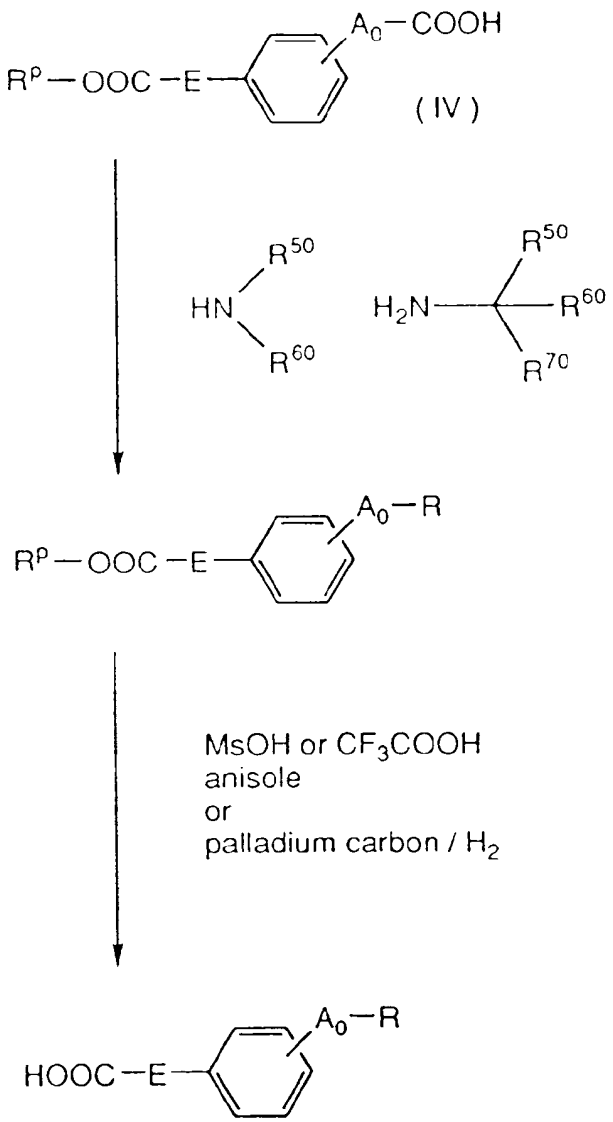
The reaction to form an amide may be carried out by the same reaction as hereinbefore defined, converting alcohol to a corresponding amine.

The reactions (1), (2) and (3) hereinbefore described may be preferably carried out in an atmosphere of inert gas (e. g., argon, nitrogen etc.) under anhydrous conditions.

The compounds of the formula (III) may be prepared by the series of reactions depicted in the following Scheme A.

Scheme (A)

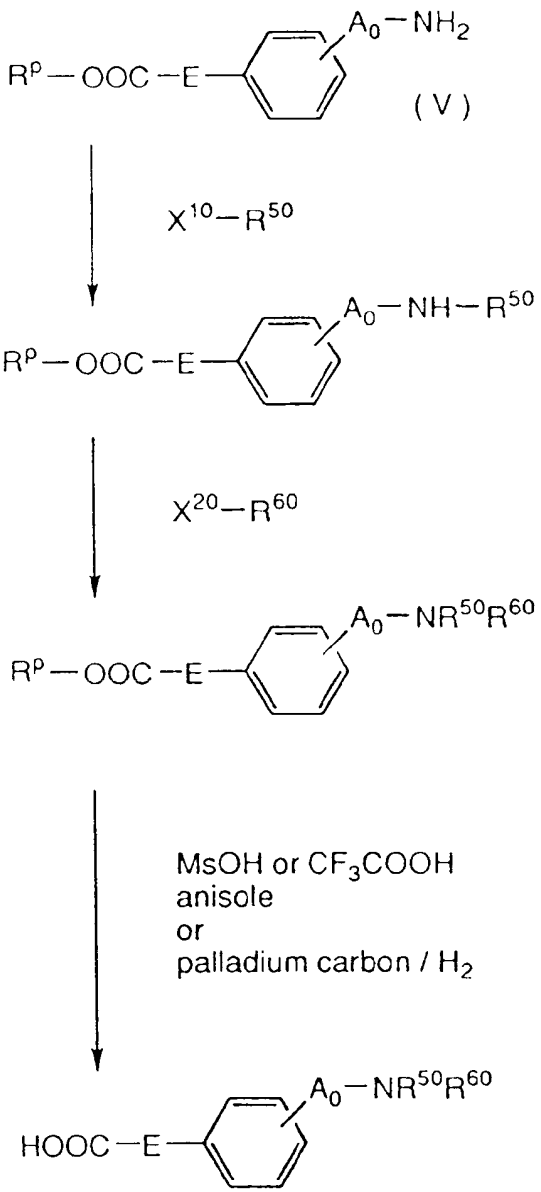
when R is (i) or (ii),



(IIIa)

Scheme (A) continued

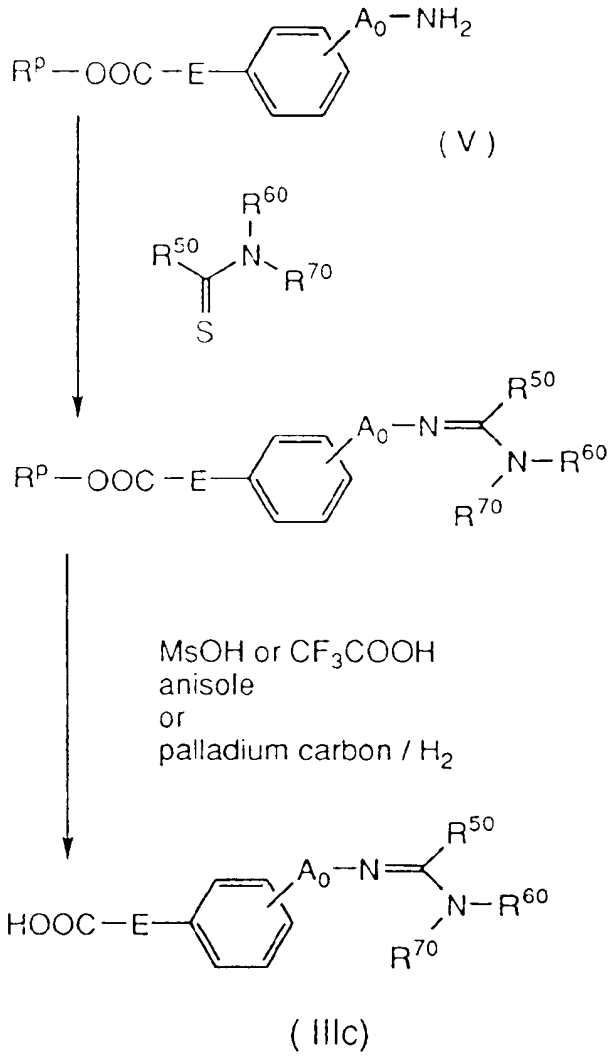
when R is (iii),



(IIIb)

Scheme (A) continued

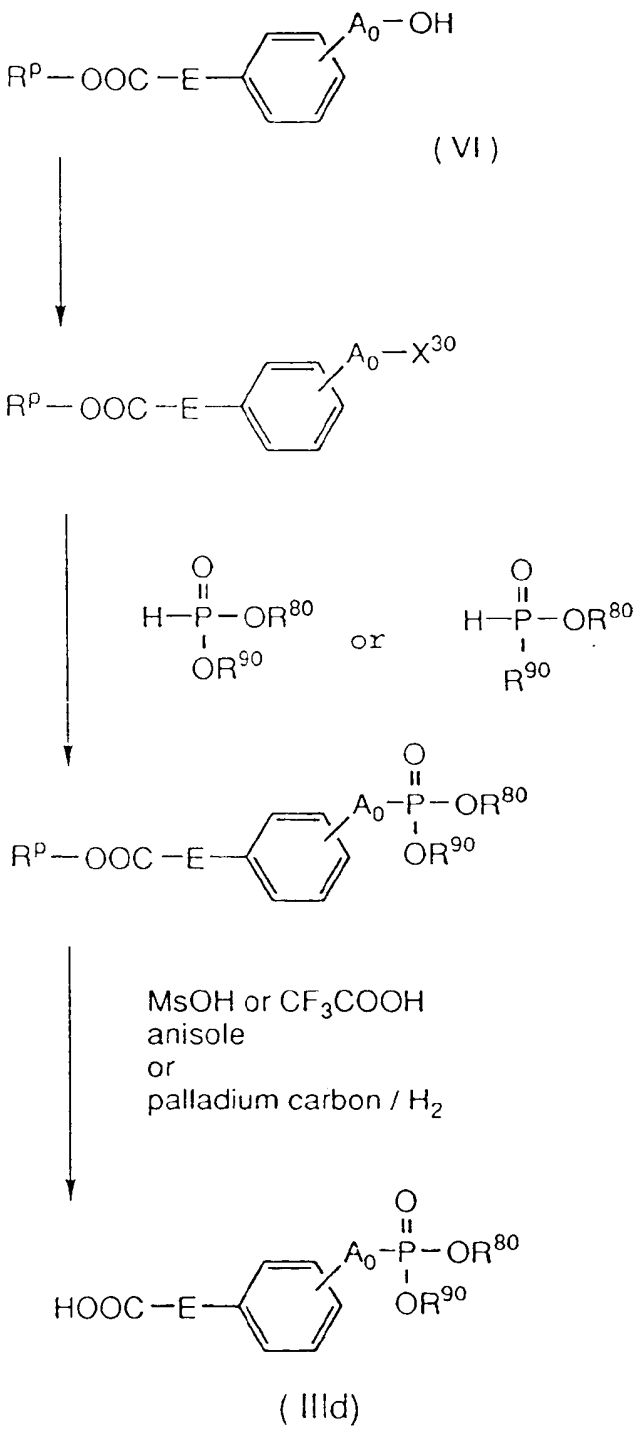
when R is (iv),



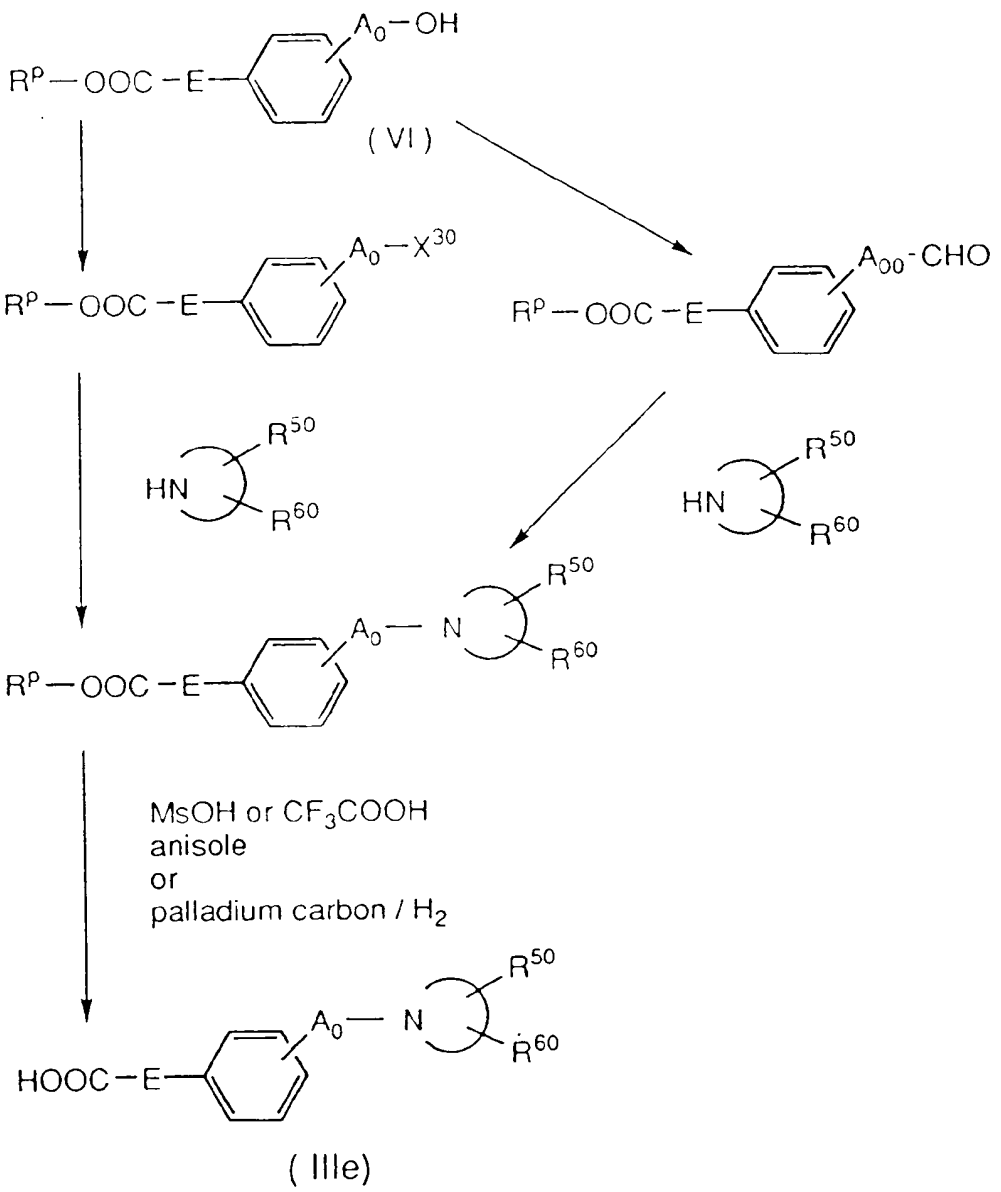
(IIIc)

Scheme (A) continued

when R is (v),



Scheme (A) continued



(IIIe)

In the Scheme A,

R^P is t-butyl or benzyloxycarbonyl,

X^{10}, X^{20} and X^{30} each independently, is halogen,

Ms is methanesulfonic acid,

A_{00} is bond, C1-3 alkylene, oxy-(C1-3) alkylene, thio-(C1-3)alkylene, C2-7 alkenylene, C2-7 alkenylene which is substituted by carboxy or C1-4 alkoxycarbonyl, and the other symbols have the same meaning as hereinbefore described.

The reactions in Schemes hereinbefore depicted may be carried out by methods known per se. The compounds of the formulae (II), (IV), (V) and (VI) used as starting materials in the Schemes hereinbefore depicted, are known per se or may be easily prepared by methods known per se.

Other starting materials and each reagents are known per se or may be prepared by known methods.

In each reaction in the present specification, products may be purified by conventional manner. For example, it may

be carried out by distillation at atmospheric or reduced pressure, high performance liquid chromatography, thin layer chromatography or column chromatography using silica gel or magnesium silicate, washing or recrystallization. Purification may be carried out after each reaction, or after a series of reactions.

[Effect]

As mentioned above, it is considered that LTB_4 antagonist is useful for anti-inflammatory and anti-allergic agent.

Therefore, the compounds of the present invention of the formula (IA) and (IB), having LTB_4 antagonistic activity, may be used for the treatment of an animal, preferably a human, as anti-inflammatory and anti-allergic agent.

It is known that an LTB_4 antagonist is also useful for the treatment of e.g. rheumatoid arthritis, inflammatory bowel diseases, psoriasis, nonsteroidal anti-inflammatory agent-induced stomach diseases, adult respiratory distress syndrome, cardiac infarction, allergic rhinitis, hemodialysis-induced neutropenia, anaphase asthma in an animal, preferably a human; an LTB_4 antagonist may be used for their prevention and/or treatment.

The compounds of the formula (IB) also have inhibitory activity on phospholipase and inhibitory activity on trypsin, in an animal, preferably a human; therefore the compounds of the formula (IB) are useful for the prevention and/or the treatment of e.g. various inflammatory, allergic diseases, disseminated intravascular coagulation, pancreatitis, severity in pancreatitis and multiple organ failure.

It is confirmed that the toxicity of the active ingredients and non-toxic salts thereof and non-toxic acid addition salts thereof in the present invention is very weak. For example, LD_{50} of Compound 1 was 117mg/kg when administered intravenously to male mice. Accordingly, the active substances in the present invention may be considered to be sufficiently safe and suitable for pharmaceutical use.

For the purpose hereinbefore described, the active ingredient in the present invention and non-toxic salts thereof and non-toxic acid addition salts thereof may be normally administered systemically or partially, usually by oral or parenteral administration.

The doses to be administered are determined depending upon age, weight, symptom, the desired therapeutic effect, the route of administration, and the duration of the treatment etc. In the human adult, the doses per person per dose are generally between 1 mg and 1000mg, by oral administration, up to several times per day, or between 100μg and 100mg, by parenteral administration (preferably, intravenously) up to several times per day. As mentioned above, the doses to be used depend upon various conditions. Therefore, there are cases in which doses lower than or greater than the ranges specified above may be used.

When administering of the compounds of the present invention, it is used in the form of solid compositions, liquid compositions or other compositions for oral administration, as injections, liniments or suppositories etc. for parenteral administration.

Solid compositions for oral administration include compressed tablets, pills, capsules, dispersible powders, and granules.

In such compositions, one or more of the active compound(s) is or are admixed with at least one inert diluent (such as lactose, mannitol, glucose, hydroxypropyl cellulose, microcrystalline cellulose, starch, polyvinylpyrrolidone, magnesium metasilicate aluminate etc.).

These compositions may also comprise, as in normal practice, additional substances other than inert diluents: e.g. lubricating agents (such as magnesium stearate, etc.), disintegrating agents (such as cellulose calcium glycolate, etc.), assisting agents for dissolving (such as arginine, glutamic acid, asparaginic acid, etc.) and stabilizer (human serum albumin, lactose, etc.).

The tablets or pills may, if desired, be coated with a film of gastric or enteric material (such as sugar, gelatin, hydroxypropyl cellulose, hydroxypropylmethyl cellulose phthalate etc.).

Capsules include hard capsules and soft capsules.

Liquid compositions for oral administration include solutions, emulsions, suspensions, syrups and elixirs.

These liquid compositions may comprise inert diluents commonly used in the art (purified water, ethanol etc.).

Besides inert diluents, such compositions may also comprise adjuvants (such as wetting agents, suspending agents, etc.), sweetening agents, flavoring agents and preserving agents.

Other compositions for oral administration include spray compositions which may be prepared by known methods and which comprise one or more of the active compound(s). Spray compositions may comprise additional substances other than inert diluents: e.g. stabilizing agents (sodium sulfate etc.), isotonic stabilizing agents (sodium chloride, sodium citrate, citric acid, etc.). For preparation of such spray compositions, for example, the method described in the United States Patent No. 2,868,691 or 3,095,355 may be used.

Injections for parenteral administration include sterile aqueous or non-aqueous solutions, suspensions and emulsions.

In such compositions, one or more of active compound(s) is or are admixed with at least one of inert aqueous diluent (s) (distilled water for injection, physiological salt solution etc.) or inert non-aqueous diluent(s) (propylene glycol, poly-

ethylene glycol, olive oil, ethanol, POLYSORBATE80 (registered trade mark) etc)

Injections may comprise furthermore assisting agents such as preserving agents, wetting agents, emulsifying agents, dispersing agents, stabilizing agents (such as human serum albumine, lactose, etc) and assisting agents for dissolving (arginine, glutamic acid, asparaginic acid, polyvinylpyrrolidone etc).

Usually, they may be sterilized by filtration (a bacteria-retaining filter, etc), by incorporation of sterilizing agents in the compositions or by irradiation, or after treated, they may also manufactured in the form of sterile solid compositions, for example, by freeze-drying, and which may be dissolved in sterile water or some other sterile diluent(s) for injection immediately before used, and which may be used.

[Example]

The following reference Examples and Examples illustrate the present invention.

The solvents in parentheses show the developing or eluting solvents and the ratios of the solvents used are by volume in chromatographic separations.

Example 1 (A): Binding inhibition against 3H-LTB4 on the human polymorphonuclear leukocyte (PMN)

Polypropylene tubes were added 0.049 ml Hanks balanced salt solution (HBSS), 0.001 ml test compound and 0.05 ml ^{3}H-LTB$_4$ (4nM), and mixed. The reaction was started by addition of thoroughly mixed cell suspension (1.6×10^6 cells), followed by incubation at 0°C for 20 min. The reaction was terminated by the addition of ice-cold HBSS (2.5 ml). PMNs were harvested by vacuum filtration through Whatman GF/C glass fiber filters on Brandel cell harvester (BRANDEL, M-24R). The filters were then washed 2 times to remove free ^{3}H-LTB$_4$ with 2.5 ml of the ice-cold PBS (-) solution. The filters were transferred to each vial, and equilibrated after adding 8 ml ACS II cocktail (Amersham). The radioactivity was measured by liquid scintillation counter (Aloka, LSC-5100).

Specific binding of ^{3}H-LTB$_4$ to receptor was defined as total binding subtracting nonspecific binding. Nonspecific binding was determined as binding in the presence of 1.5μM LTB$_4$ instead of test compound.

The inhibitory effect of test compound was calculated from the following equation.

The percentage of inhibition (%) = $100 - (B_1/B_0 \times 100)$

B_1 : Specific ^{3}H-LTB$_4$ binding in presence of test compound

B_0 : Specific ^{3}H-LTB$_4$ binding in absence of test compound

[Results]

The results are shown in the following Table 17.

Table 17

Compound No.	European Patent Publication No. 588655 Compound (Example No.)	binding activity (%)
1	1 (i)	91.5
2	1 (m)	76.6
3	1 (p)	75.0
4	1 (aa)	63.7
5	1 (ii)	94.3
6	1 (pp)	71.6
7	1 (qq)	78.0
8	1 (hhh)	82.7
9	1 (lll)	91.6
10	1 (mmm)	86.5
11	2 (g)	76.8
12	2 (p)	95.2
13	2 (u)	100.2
14	2 (w)	96.5
15	2 (cc)	89.1
16	2 (gg)	83.6
17	2 (kk)	93.9

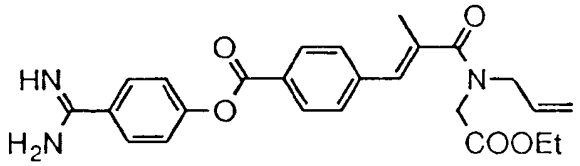
Continuation of the Table on the next page

Table 17 (continued)

Compound No.	European Patent Publication No. 588655 Compound (Example No.)	binding activity (%)
18	3 (f)	87.0
19	4	74.0
20	4 (a)	83.5
21	5 (r)	90.8
22	5 (w)	89.7
23	5 (ff)	78.0
24	European Patent Publication No. 656349 Example 1 (b)	61.2

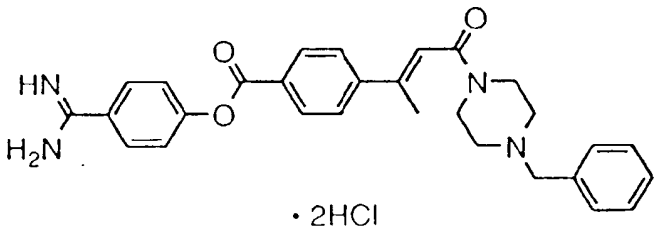
The structure of compounds used in the present invention are shown below.

Compound No.1



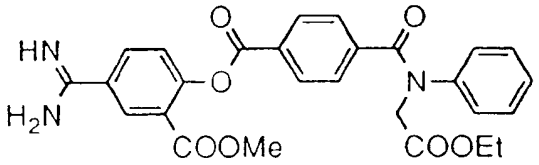
• MsOH

Compound No.2



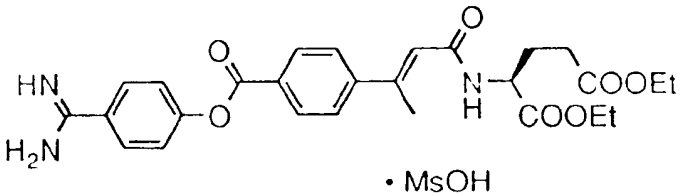
• 2HCl

Compound No.3



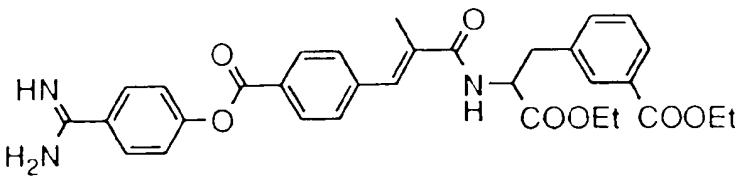
• AcOH

Compound No.4



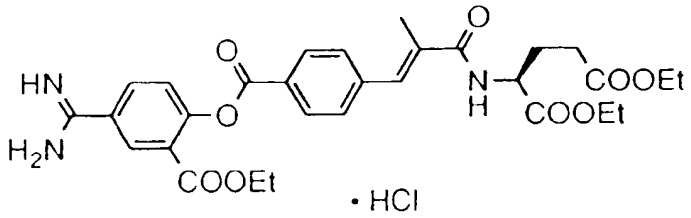
• MsOH

Compound No.5



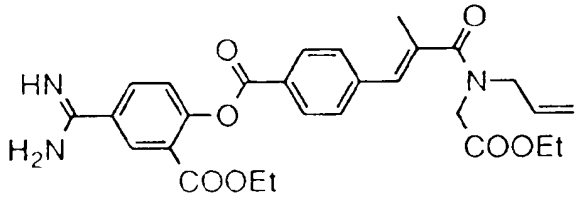
• MsOH

Compound No.6



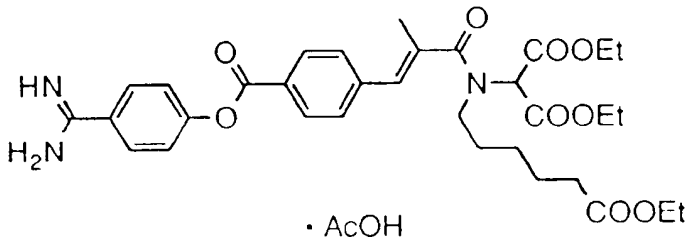
• HCl

Compound No.7



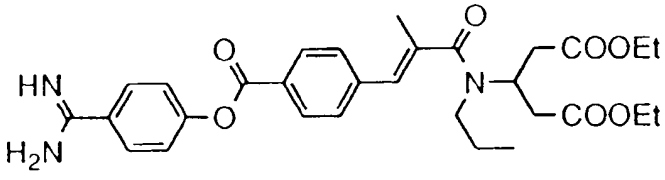
• HCl

Compound No.8



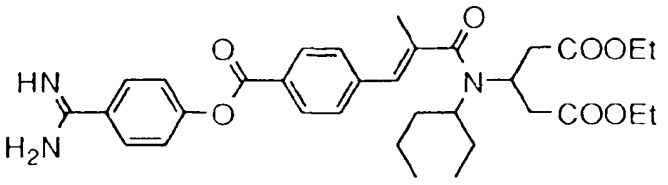
• AcOH

Compound No.9



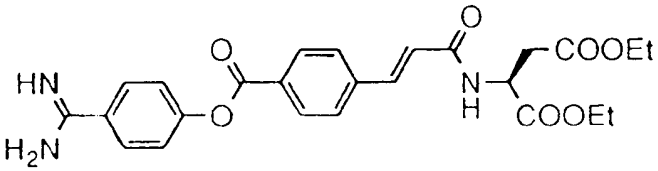
• AcOH

Compound No.10



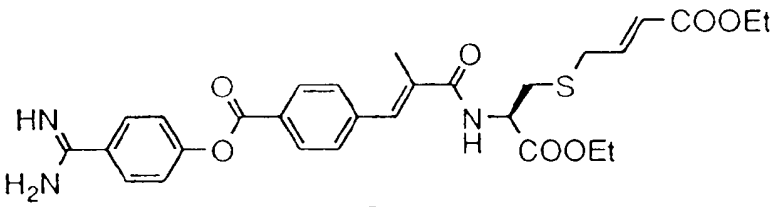
• AcOH

Compound No.11



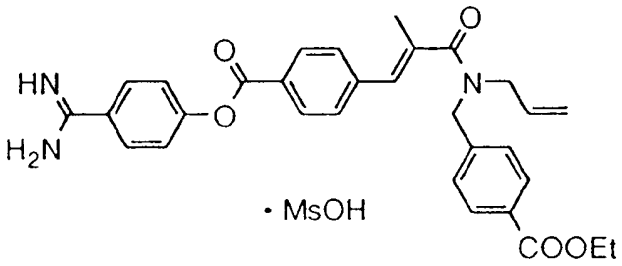
• HCl

Compound No.12



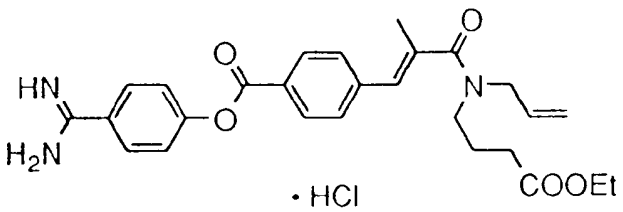
• MsOH

Compound No.13



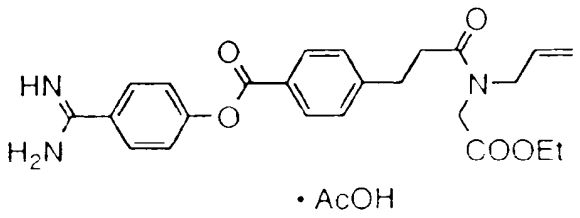
• MsOH

Compound No.14



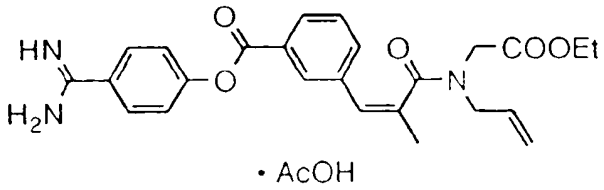
• HCl

Compound No.15



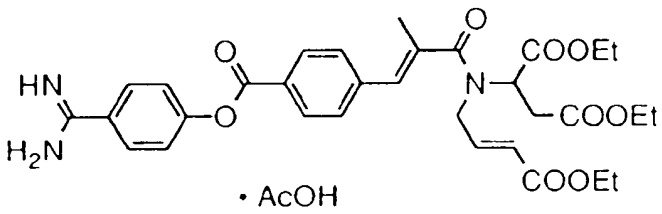
• AcOH

Compound No.16



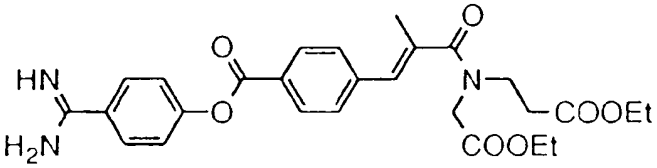
• AcOH

Compound No.17



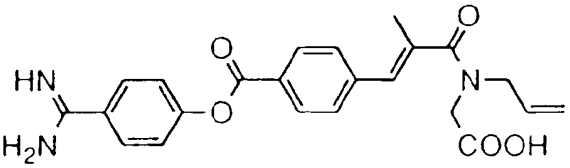
• AcOH

Compound No.18



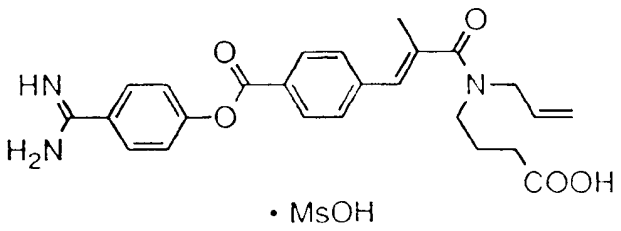
• AcOH

Compound No.19



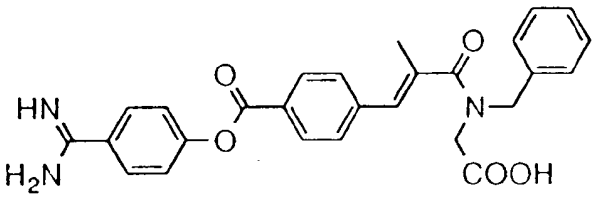
• 2MsOH

Compound No 20



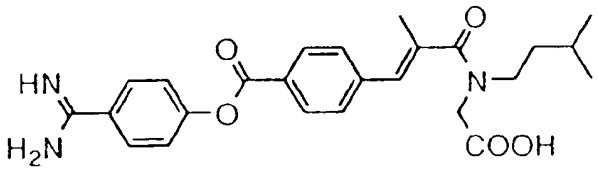
• MsOH

Compound No.21



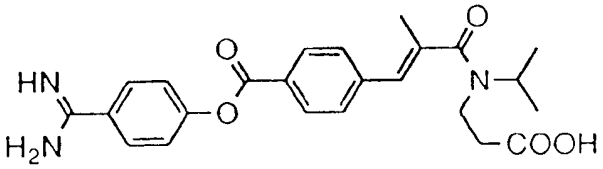
• MsOH

Compound No.22



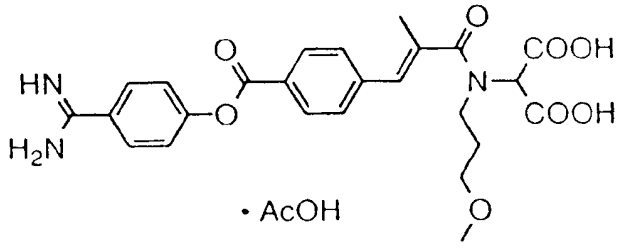
• MsOH

Compound No.23



• MsOH

Compound No.24



• AcOH

Example 1(B):

The compounds of the formula (IB), of the present invention have an antagonistic activity on LTB_4. The results which are measured by method as hereinbefore described in Example 1 (A), are shown the following Table 18.

Table 18

Compound (Example No.)	binding activity (%)
2	79.7
2 (a)	92.0
2 (b)	97.9
2 (c)	103.2
2 (d)	99.3
2 (e)	94.5
2 (f)	91.8
2 (g)	89.6
2 (h)	85.4
2 (i)	69.6
2 (j)	55.4
2 (k)	97.7
2 (l)	81.0
2 (m)	89.2
2 (n)	82.8
2 (o)	85.8
2 (p)	95.2
2 (q)	98.0
2 (r)	80.1

Table 18 continued

Compound (Example No.)	binding activity (%)
2 (s)	83.0
2 (t)	51.5
2 (u)	67.6
2 (v)	92.0
2 (w)	76.7
2 (x)	94.1
2 (y)	85.5
2 (z)	92.8
2 (aa)	94.4
2 (bb)	87.3
2 (cc)	76.7
2 (dd)	50.8
2 (ee)	65.3
2 (ff)	82.4
3	96.8
4	73.1
4 (a)	52.0
5	89.7
5 (a)	62.5
5 (b)	90.2
6	67.8

Example 1 (C): inhibitory activity on phospholipase A_2 and on trypsin

It has been confirmed that the compounds of the formula (IB), of the present invention have inhibitory activities on phospholipaseA_2 (PLA_2) and on trypsin.

For example, in laboratory tests the following results were obtained.

[Method]

(1) Inhibitory activity on PLA_2

A reaction solution including 50 mM tris-HCl buffer (pH7.5, 874µl; containing 100mM sodium chloride, 1mM EDTA), 1M calciumchloride (6µl), 1% bovine serum albumin (10µl) and 2.5mM 10PY-PC (10µl), was prepared. To the solution were added a test compound in various concentration or water (50µl), and a solution of 10mU/ml PLA_2 (derived from hog pancreas) (50µl). The appearance of fluorescence was measured (Ex=345 nm, Em=396 nm). Percentage (%) of the strength of fluorescence in the presence of a test compound was calculated when the strength of that in the absence thereof was regarded as 100%, and therefrom IC_{50} value was calculated. The results are shown in the following Table19.

(2) Inhibitory activity on trypsin

To a mixture of a 0.2 M HEPES • sodium hydroxide buffer solution (pH 8.0, 100µl) and distilled water (640µl), were added a test compound in various concentration or water (10µl), and a solution of 80 mU/ml trypsin (derived from bovine pancreas) (50µl) and then the mixture was preincubated for one minute at 30°C. To the solution thus obtained was added 2.5mM BAPNA (200µl) and the mixture was incubated at 30°C. The absorbance at 405 nm was measured. Percentage (%) of the absorbance in the presence of a test compound was calculated when the absorbance in the absence thereof was regarded as 100%, and therefrom IC_{50} value was calculated. The results

are shown in the following Table 19.

Table 19

Compound (Example No)	inhibitory activity on PLA_2 IC_{50} (μM)	inhibitory activity on trypsin IC_{50} (μM)
2	--	0.19
2 (a)	2.6	0.4
2 (b)	3.8	0.56
2 (c)	8.1	0.26
2 (d)	8.7	0.14
2 (e)	8.5	0.34
2 (f)	70	0.10
2 (g)	53	0.16
2 (h)	11	0.15
2 (i)	59	0.14
2 (j)	--	0.12
2 (k)	20	0.10
2 (l)	94	0.12
2 (m)	18	0.17
2 (n)	10	0.16
2 (o)	12	0.14
2 (p)	29	0.13
2 (q)	34	0.16
2 (r)	46	0.16
2 (s)	44	0.16
3	4.7	0.12
4	41	0.16
4 (a)	--	0.14
5	--	0.13
5 (a)	--	0.15
6	4.5	0.17

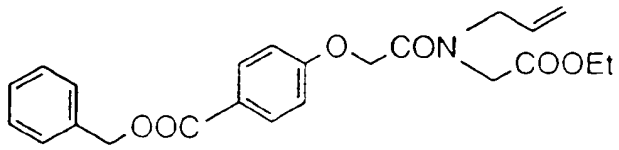
In the methods hereinbefore described,
10PY-PC represents 3' -palmitoyl-2-(1-pyrenedecanoyl)-L-α-phosphatidylcholine,
HEPES represents 4-2-hydroxyethyl)-1-piperazineethanesulfonic acid, and
BAPNA represents α-N-benzoyl-DL-arginine-p-nitroanilide hydrochloride.

[Preparation of new compounds]

The following reference Examples and Examples illustrate new compounds of the formula (IB).

Reference Example 1

N-(2-Propenyl)-N-ethoxycarbonylmethyl-4-benzyloxycarbonylphenoxyacetamide.

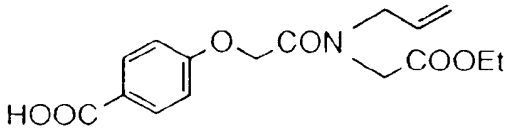


A solution of 4-benzyloxycarbonylphenoxyacetic acid (4.29g) in thionyl chloride (10ml) was refluxed for 15min. After an excess amount of solvent was distilled off, product was dissolved in dichloromethane. And this solution was added dropwise to a solution of N-(2-propenyl)-N-ethoxycarbonylmethylamine (2.14g) in pyridine under cooling with ice. After

the solution was stirred for 30min at room temperature, the solution was poured into ice water. The mixture was extracted with ethyl acetate. The extract was washed with a solution of 1N hydrochloric acid, water and a saturated aqueous solution of sodium chloride, successively, evaporated. The residue purified by silica gel column chromatograhy to give the title compound (5.96g) having the following physical data:
TLC : Rf 0.43 (hexane : ethyl acetate=3 : 2)

Reference Example 2

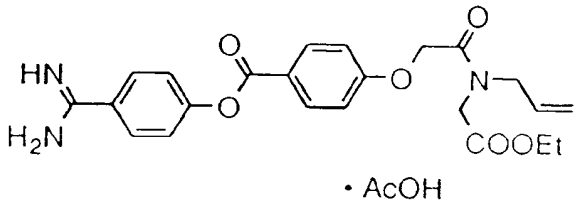
N-(2-Propenyl)-N-ethoxycarbo nyl methyl-4-carboxyphenoxyacetamide



Methanesulfonic acid (28ml) was added to the compound prepared in Reference Example 1 (5.69g) under cooling at 0°C. After reaction solution was stirred for one hour at room temperature, poured into ice water and extracted with ethyl acetate. Organic layer was washed with water, and a saturated aqueous solution of sodium chloride, successively, evaporated. The residue was purified by silica gel column chromatography to give the title compound (4.31g) having the following physical data.
TLC : Rf 0.35 (hexane : ethyl acetate=1 : 1)

Example 2

N-(2-propenyl)-N-ethoxycarbonylmethyl-4-(4-amidinophenoxycarbonyl)phenoxyacetamide acetate

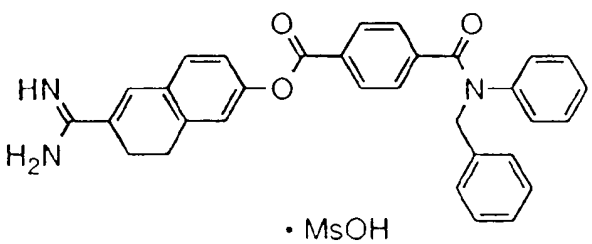


To a solution of amidinophenol (1.72g) and the compound prepared in Reference Example 2 (3.21g) in pyridine was add DCC (3.09g) and stirred overnight at room temperature. Reaction solution was filtered and the filtrate was evaporated. The residue was purified by silica gel column chromatography and was formed into acetate by conventional manner to obtain the title compound having the following physical data.
TLC : Rf 0.41 (chloroform : methanol : acetic acid =10 : 2 : 1), NMR (CD_3OD) : δ 8.14(2H, d, J=9.0Hz), 7.90(2H, d, J=9.0Hz), 7.49(2H, d, J=9.0Hz), 7.08(2H, d, J=9.0Hz), 5.68-6.07(1H, m), 5.17-5.37(2H, m), 4.93 and 5.02(2H, s, ratio=7 : 10), 4.03-4.28(6H, m), 1.26 and 1.29(3H, t, J=7.0Hz).

Example 2 (a)~2 (ff)

By the same procedure as Reference Example 1,2 and Example 2, the compound having the following physical data was given.

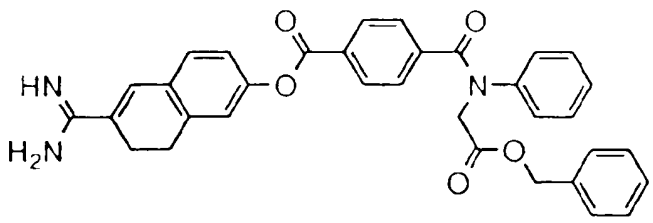
Example 2 (a)



TLC : Rf 0.57 (chloroform : methanol :acetic acid = 10 : 2 : 1),

NMR (CD_3OD) : δ 2.60(2H, t, J=8.0Hz), 2.98(2H, t, J=8.0Hz), 5.17(2H, s), 6.99-7.02(2H, m), 7.09-7.16(5H, m), 7.30(5H, s), 7.38(1H, d, J=9.0Hz), 7.43(1H, s), 7.48(2H, d, J=8.0Hz), 7.98(2H, d, J=8.0Hz).

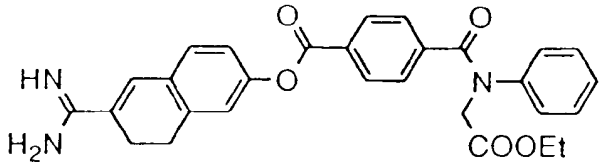
Example 2 (b)



• AcOH

TLC : Rf 0.60 (chloroform : methanol : acetic acid = 10 : 2 : 1),
NMR (CD_3OD) : δ 2.41 (2H, t, J=7.0Hz), 3.00(2H, t, J=7.0Hz), 4.69(2H, s), 5.23(2H, s), 7.09-7.42(14H, m), 7.43(2H, d, J=8.0Hz), 7.98(2H, d, J=8.0Hz).

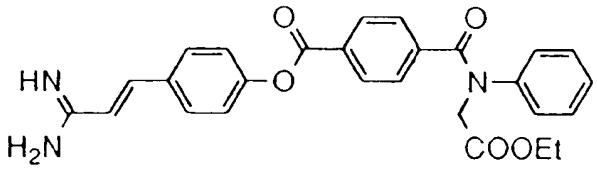
Example 2 (c)



• HCl

TLC : Rf 0.53 (chloroform : methanol :acetic acid = 10 : 2 : 1).
NMR (CD_3OD) : δ 8.0(2H, d, J=8.0Hz), 7.50(2H, d, J=8.0Hz), 7.46(1H, s), 7.40(1H, d, J=8.0Hz), 7.24(5H, s), 7.12(1H, s), 7.10(1H, d, J=8.0Hz), 4.61(2H, s), 4.22(2H, q, J=8.0Hz), 3.00(2H, t, J=9.0Hz), 2.61(2H, t, J=9.0Hz), 1.30(3H, t, J=8.0Hz).

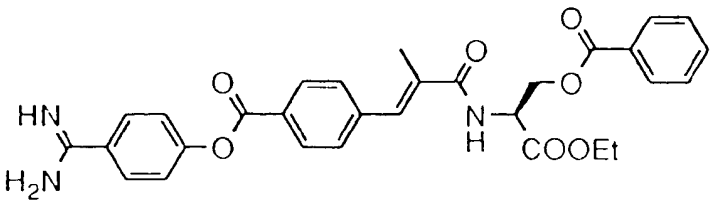
Example 2 (d)



• AcOH

TLC : Rf 0.45 (chloroform : methanol : acetic acid = 10 : 2 : 1),
NMR (CD_3OD) : δ 8.00(2H, d, J=8Hz), 7.80(1H, d, J=16Hz), 7.75(2H, d, J=8Hz), 7.50(2H, d, J=8Hz), 7.35(2H, d, J=8Hz), 7.30-7.20(5H, m), 6.70(1H, d, J=16Hz), 4.65(2H, s), 4.25(2H, q, J=7Hz), 1.30(3H, t, J=7Hz).

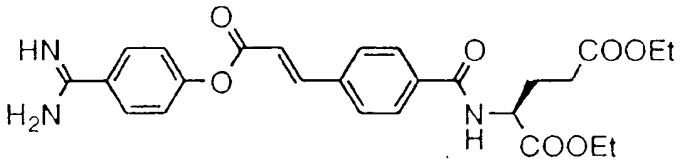
Example 2 (e)



• AcOH

TLC : Rf 0.45 (chloroform : methanol :acetic acid = 10 : 2 : 1),
NMR (CD_3OD) : δ 1.30(3H, t, J=7.0Hz), 2.18(3H, s), 4.31(2H, q, J=7.0Hz), 4.77(2H, m), 5.02(1H, t, J=4.0Hz), 7.39-7.61 (8H, m), 7.89(2H, d, J=9.0Hz), 8.02(2H, d, J=9.0Hz), 8.22(2H, d, J=9.0Hz).

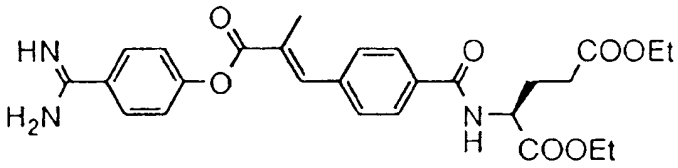
Example 2 (f)



• HCl

TLC : Rf 0.43 (chloroform : methanol :acetic acid = 10 : 2 : 1),
NMR (CD_3OD) : δ 8.00-7.80(7H, m), 7.50(2H, d, J=8.5Hz), 6.90(1H, d, J=16Hz), 4.60(1H, dd, J=4.5, 4.5Hz), 4.20(2H, q, J=6.5Hz), 4.15(2H, q, J=6.5Hz), 2.50(2H, t, J=7.5Hz), 2.30(1H, m), 2.10(1H, m), 1.30(3H, t, J=6.5Hz), 1.25(3H, t, J=6.5Hz).

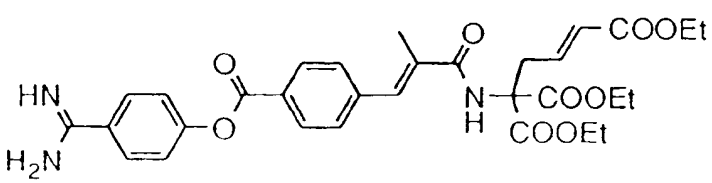
Example 2 (g)



• HCl

TLC : Rf 0.46 (chloroform : methanol :acetic acid = 10 : 2 : 1),
NMR (CD_3OD) : δ 8.00-7.90(5H, m), 7.65(2H, d, J=8Hz), 7.50(2H, d, J=8Hz), 4.65(1H, dd, J=4.5, 4.5Hz), 4.20(2H, q, J=6.5Hz), 4.15(2H, q, J=6.5Hz), 2.50(2H, t, J=7.5Hz), 2.30(1H, m), 2.25(3H, m), 2.10(1H, m), 1.30(3H, t, J=6.5Hz), 1.25 (3H, t, J=6.5Hz).

Example 2 (h)

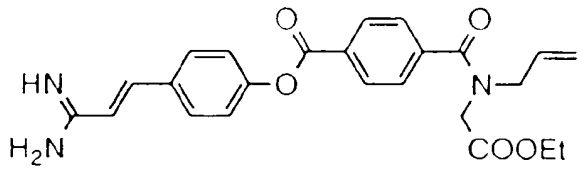


• HCl

TLC : Rf 0.48 (chloroform : methanol : acetic acid = 15 : 2 : 1),

NMR (CD_3OD) δ 8.24(2H, d, J=8.5Hz), 7.95(2H, d, J=8.5Hz), 7.62(2H, d, J=8.0Hz), 7.55(2H, d, J=8.0Hz), 7.35(1H, s), 6.85(1H, dt, J=7.5, 15.0Hz), 5.93(1H, d, J=15.0Hz), 4.28(4H, q, J=7.5Hz), 4.18(2H, d, J=7.5Hz), 3.23(2H, d, J=7.5Hz), 2.14(3H, s), 1.26(6H, t, J=7.5Hz), 1.23(3H, t, J=7.5Hz)

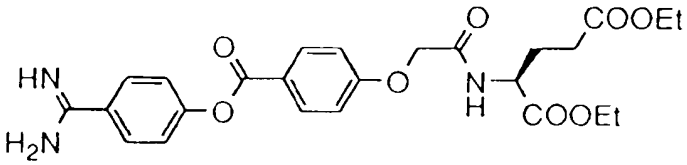
Example 2 (i)



• AcOH

TLC : Rf 0.43 (chloroform : methanol : acetic acid = 10 : 2 : 1),
NMR (CD_3OD) : δ 8.24 and 8.26(2H, d, J=9.0Hz), 7.81(1H, d, J=18.0Hz), 7.75(2H, d, J=9.0Hz), 7.58 and 7.66(2H, d, J=9.0Hz), 7.37(2H, d, J=9.0Hz), 6.73(1H, d, J=18.0Hz), 5.77-5.96(1H, m), 5.22-5.34(2H, m), 4.12-4.28(4H, m), 3.96-4.00 (2H, m), 1.20 and 1.30(3H, t, J=7.0Hz).

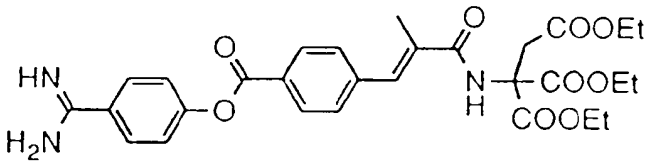
Example 2 (j)



• AcOH

TLC : Rf 0.44 (chloroform : methanol : acetic acid = 10 : 2 : 1),
NMR (CD_3OD) : δ 8.18(2H, d, J=9.0Hz), 7.90(2H, d, J=9.0Hz), 7.50(2H, d, J=9.0Hz), 7.17(2H, d, J=9.0Hz), 4.70(2H, s), 4.55(1H, dd, J=9.5, 5.0Hz), 4.18(2H, q, J=7.0Hz), 4.11(2H, q, J=7.0Hz), 2.40(2H, t, J=7.0Hz), 1.97-2.32(2H, m), 1.27 (3H, t, J=7.0Hz), 1.23(3H, t, J=7.0Hz).

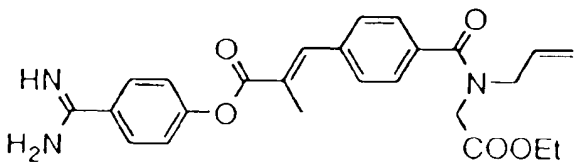
Example 2 (k)



• HCl

TLC : Rf 0.48 (chloroform : methanol : acetic acid = 15 : 2 : 1),
NMR (CD_3OD) : δ 8.22(2H, d, J=8.0Hz), 7.92(2H, d, J=8.0Hz), 7.60(2H, d, J=8.0Hz), 7.56(2H, d, J=8.0Hz), 7.37(1H, brs), 4.27(4H, q, J=7.5Hz), 4.13(2H, q, J=7.5Hz), 3.47(2H, s), 2.16(3H, s), 1.25(6H, t, J=7.5Hz), 1.22(3H, t, J=7.5Hz).

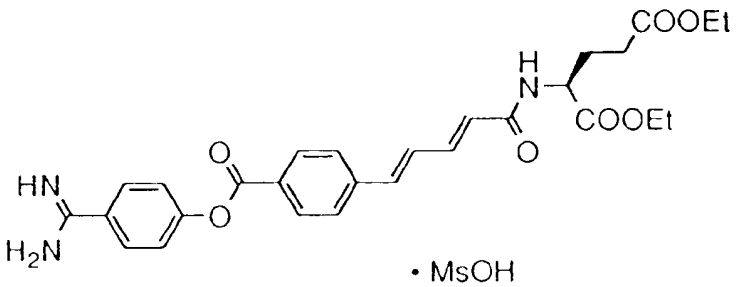
Example 2 (l)



• AcOH

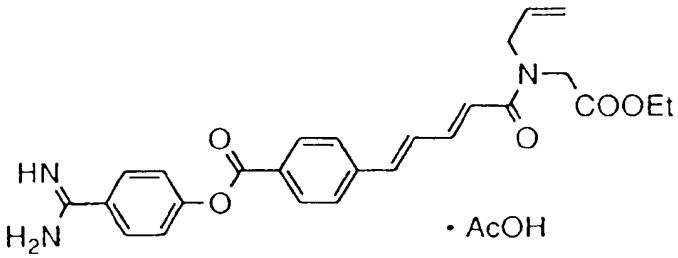
TLC : Rf 0.49 (chloroform : methanol :acetic acid = 10 : 2 : 1),
NMR (CD_3OD) : δ 7.98(1H, s), 7.90(2H, d, J=9.0Hz), 7.58(4H, m), 7.48(2H, d, J=9.0Hz), 5.78-5.96(1H, m), 5.23-5.32 (2H, m), 4.22(2H, q, J=7.0Hz), 4.20(2H, s), 3.98-4.03(2H, m), 2.24(3H, s), 1.30(3H, t, J=7.0Hz).

Example 2 (m)



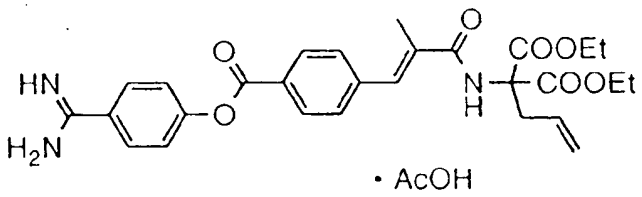
TLC : Rf 0.38 (chloroform : methanol : acetic acid = 10 : 1 : 1),
NMR (CD_3OD) : δ 8.20(2H, d, J=8.4Hz), 7.92(2H, d, J=8.8Hz), 7.74(2H, d, J=8.4Hz), 7.55(2H, d, J=8.8Hz), 7.25(3H, m), 6.32(1H, d, J=14.6Hz), 4.55(1H, m), 4.20(2H, q, J=7.2Hz), 4.14(2H, q, J=7.0Hz), 2.72(3H, s), 2.45(2H, t, J=7.4Hz), 2.36-1.90(2H, m), 1.29(3H, t, J=7.2Hz), 1.25(3H, t, J=7.0Hz).

Example 2 (n)



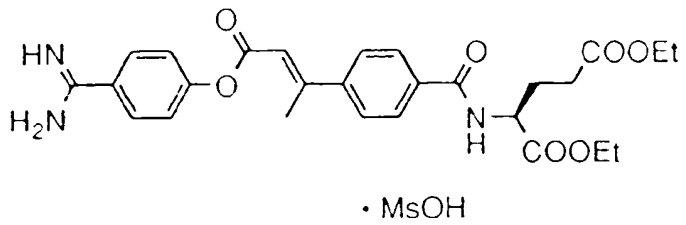
TLC : Rf 0.39 (chloroform : methanol :acetic acid = 10 : 1 : 1),
NMR (CD_3OD) : δ 8.18(2H, d, J=8.4Hz), 7.92(2H, d, J=8.8Hz), 7.73(2H, d, J=8.4Hz), 7.53(2H, d, J=8.8Hz), 7.50-7.15 (2H, m), 7.05(1H, d, J=14.5Hz), 6.75-6.55(1H, m), 6.03-5.81(1H, m), 5.32-5.14(2H, m), 4.20(2H, q, J=7.2Hz), 4.30-4.10 (4H, m), 1.94(3H, s), 1.28(3H, t, J=7.2Hz).

Example 2 (o)



TLC : Rf 0.50 (chloroform : methanol :acetic acid = 10 : 2 : 1),
NMR (CD_3OD) : δ 8.20(2H, d, J=8.5Hz), 7.90(2K d, J=11.5Hz), 7.60(2H, d, J=8.5Hz), 7.55(2H, d, J=11.5Hz), 7.35(1H, br.s), 5.70(1H, m), 5.15(2H, m), 4.25(4H, q, J=7Hz), 3.10(2H, d, J=7Hz), 2.15(3H, s), 1.95(3H, s), 1.25(6H, t, J=7Hz).

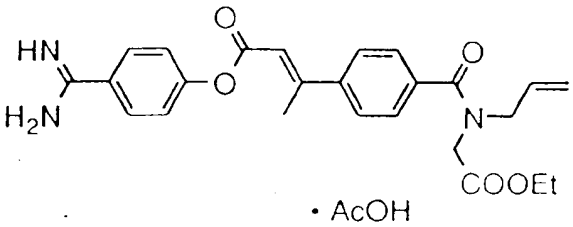
Example 2 (p)



• MsOH

TLC : Rf 0.50 (chloroform : methanol : acetic acid = 10 : 1 : 1),
NMR (CD_3OD) : δ 7.94(2H, d, J=8.0Hz), 7.89(2H, d, J=8.5Hz), 7.72(2H, d, J=8.5Hz), 7.44(2H, d, J=8.0Hz), 6.49(1H, s), 4.64(1H, m), 4.23(2H, q, J=7.5Hz), 4.14(2H, q, J=7.0Hz), 2.74(3H, s), 2.66(3H, s), 2.52(2H, t, J=7.0Hz), 2.32(2H, m), 2.14(2H, m), 1.30(3H, t, J=7.0Hz), 1.25(3H, t, J=7.5Hz).

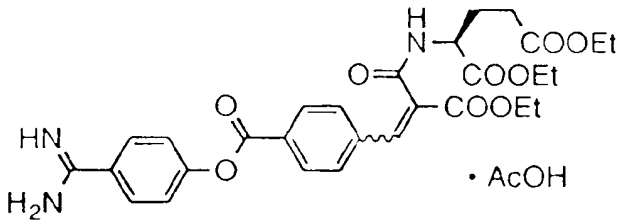
Example 2 (q)



• AcOH

TLC : Rf 0.50 (chloroform : methanol :acetic acid = 10 : 1 : 1),
NMR (CD_3OD) : δ 7.89(2H, d, J=8.8Hz), 7.73(2H, d, J=8.4Hz), 7.56(2H, d, J=8.4Hz), 7.44(2H, d, J=8.8Hz), 6.49(1H, s), 5.88(1H, m), 5.35-5.20(2H, m), 4.30-4.10(4H, m), 4.00(2H, m), 2.65(3H, s), 1.93(3H, s), 1.31(3H, t, J=7.2Hz).

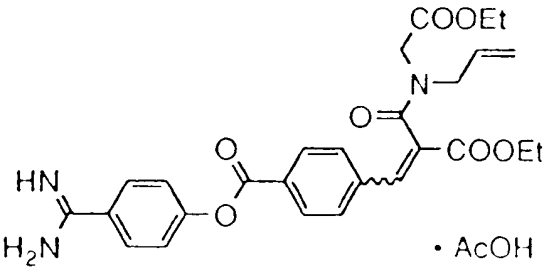
Example 2 (r)



• AcOH

TLC : Rf 0.46 (chloroform : methanol : acetic acid = 10 : 2 : 1),
NMR (CD_3OD) : δ 8.18(2H, d, J=9.0Hz), 7.93(2H, d, J=9.0Hz), 7.82(2H, d, J=9.0Hz), 7.80(1H, s), 7.52(2H, d, J=9.0Hz), 4.66(1H, dd, J=8.5Hz,4.0Hz), 4.33(2H, q, J=7.0Hz), 4.20(2H, q, J=7.0Hz), 4.12(2H, q, J=7.0Hz), 2.39(2H, t, J=7.0Hz), 2.11-2.31(1H, m), 1.82-2.00(1H, m), 1.36(3H, t, J=7.0Hz), 1.24(3H, t, J=7.0Hz), 1.21(3H, t, J=7.0Hz).

Example 2 (s)

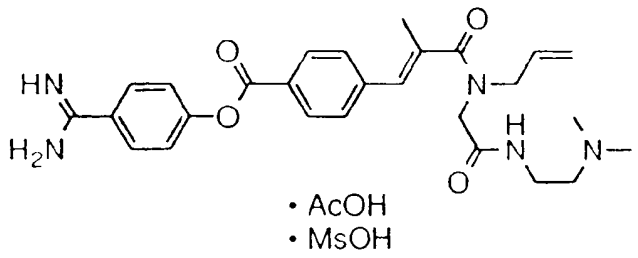


• AcOH

TLC : Rf 0.43 (chloroform : methanol : acetic acid = 10 : 2 : 1),

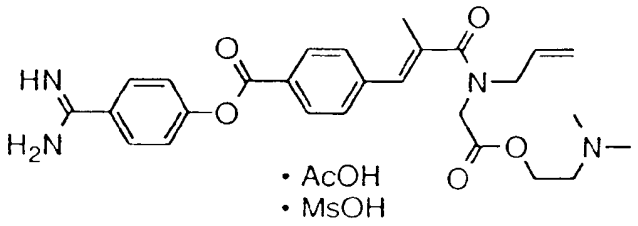
NMR (CD_3OD) : δ 8.20 and 8.22(2H, d, J=8.0Hz), 7.92(2H, d, J=9.0Hz), 7.75-7.90(1.6H, m), 7.64(1H, d, J=8.0Hz), 7.54 (2H, d, J=9.0Hz), 7.18 and 7.26(0.4H, m), 5.54-5.72(0.4H, m), 5.10-5.31(2H, m), 4.17-4.40(6H, m), 3.98(2H, br), 1.08-1.38(6H, m).

Example 2 (t)



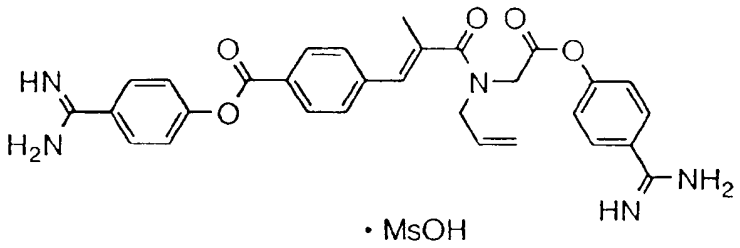
TLC : Rf 0.15 (chloroform : acetic acid : H_2O= 3 : 1 : 1),
NMR (CD_3OD) : δ 8.23(2H, d, J=8Hz), 7.93(2H, d, J=8Hz), 7.58(2H, d, J=8Hz), 7.53(2H, d, J=8Hz), 6.80(1H, bs), 6.10-5.90(1H, b), 5.35-5.20(2H, m), 4.25-4.00(4H, m), 3.68-3.45(2H, m), 3.25-3.00(2H, m), 2.88(6H, s), 2.69(3H, s), 2.15(3H, s), 1.96(3H, s).

Example 2 (u)



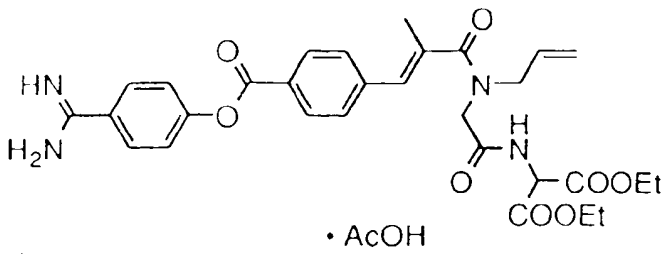
TLC : Rf 0.46 (chloroform : methanol : acetic acid = 10 : 2 : 1),
NMR (CD_3OD) : δ 8.18(2H, d, J=9.0Hz), 7.93(2H, d, J=9.0Hz), 7.82(2H, d, J=9.0Hz), 7.80(1H, s), 7.52(2H, d, J=9.0Hz), 4.66(1H, dd, J=8.5Hz,4.0Hz), 4.33(2H, q, J=7.0Hz), 4.20(2H, q, J=7.0Hz), 4.12(2H, q, J=7.0Hz), 2.39(2H, t, J=7.0Hz), 2.11-2.31(1H, m), 1.82-2.00(1H, m), 1.36(3H, t, J=7.0Hz), 1.24(3H, t, J=7.0Hz), 1.21(3H, t, J=7.0Hz).

Example 2 (v)



TLC : Rf 0.22 (chloroform : methanol :acetic acid = 10 : 2 : 1),
NMR (CD_3OD) : δ 8.21 (2H, d, J=8.0Hz), 7.95(2H, d, J=8.0Hz), 7.89(2H, d, J=8.0Hz), 7.59(2H, d, J=8.0Hz), 7.55(2H, d, J=8.0Hz), 7.43(2H, d, J=8.0Hz), 6.78(1H, s), 6.15-5.80(1H, m), 5.47-5.28(2H, m), 4.42(2H, s), 4.25(2H, d, J=5.0Hz), 2.68(3H, s, CH_3SO_3H), 2.18(3H, s).

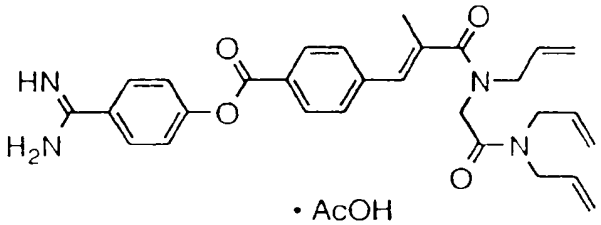
Example 2 (w)



• AcOH

TLC : Rf 0.27 (chloroform: methanol : acetic acid = 10 : 2 : 1),
NMR (CD_3OD) : δ 8.20(2H, d, J=8Hz), 7.91(2H, d, J=8Hz), 7.57(2H, d, J=8Hz), 7.53(2H, d, J=8Hz), 6.73(1H, s), 5.8-6.0 (1H, br), 5.2-5.35(2H, m), 4.8-4.9(1H, m), 4.0-4.3(8H, m), 2.12(3H, s), 1.91(3H, s)1.27(6H, t, J=7Hz).

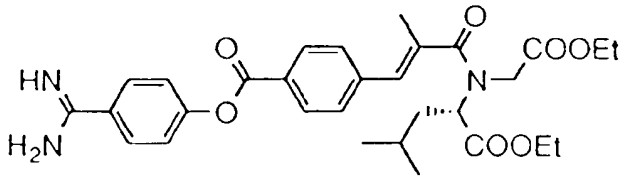
Example 2 (x)



• AcOH

TLC : Rf 0.25 (chloroform : methanol :acetic acid = 10 : 2 : 1),
NMR (CD_3OD) : δ 8.22(2H, d, J=8Hz), 7.91(2H, d, J=8Hz), 7.52 and 7.67(4H, d, J=8Hz, rotamer), 6.65 and 6.78(1H, s, rotamer), 5.6-6.0(3H, br), 5.0-5.3(6H, m), 3.9-4.4(8H, m), 2.11 and 2.16(3H, s, rotamer), 1.92(3H, s).

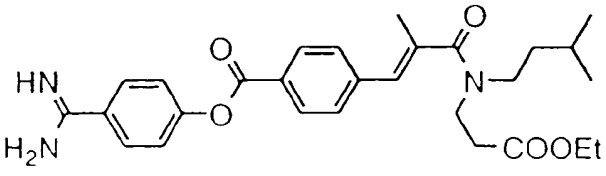
Example 2 (y)



• HCl

TLC : Rf 0.41 (chloroform : methanol : acetic acid = 20 : 2 : 1),
NMR (CD_3OD) : δ 8.22(2H, d, J=8.0Hz), 7.94(2H, d, J=8.0Hz), 7.55(4H, t, J=7.5Hz), 6.71(1H, brs), 5.20-4.90(1H, m), 4.40-4.00(6H, m), 2.20-2.00(3H, m), 1.95-1.50(3H, m), 1.30(6H, t, J=7.5Hz), 1.10-0.80(6H, m).

Example 2 (z)

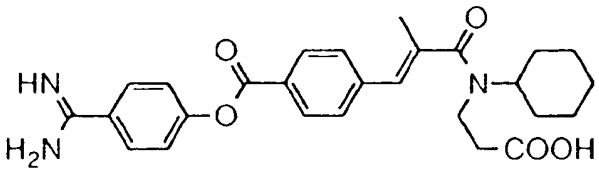


• HCl

TLC : Rf 0.40 (chloroform : methanol : acetic acid = 20 : 2 : 1),

NMR (CD_3OD) : δ 8.21(2H, d, J=8.5Hz), 7.95(2H, d, J=8.5Hz), 7.57(4H, t, J=8.0Hz), 6.62(1H, s), 4.15(2H, q, J=7.0Hz), 3.80-3.60(2H, m), 3.55-3.38(2H, m), 2.68(2H, t, J=7.5Hz), 2.12(3H, s), 1.70-1.40(3H, m), 1.27(3H, t, J=7.5Hz), 1.10-0.70 (6H, m).

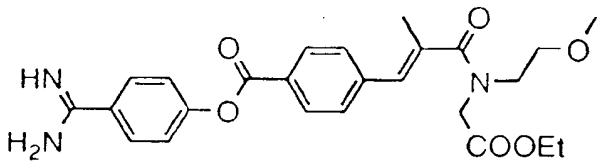
Example 2 (aa)



• CF_3COOH

TLC : Rf 0.55 (chloroform : methanol :acetic acid = 10 : 2 : 1),
NMR (CD_3OD) : δ 8.23(2H, d, J=8Hz), 7.93(2H, d, J=8Hz), 7.57(2H, d, J=8Hz), 7.54(2H, d, J=8Hz), 6.60(1H, s), 3.92-3.50 (3H, m), 2.70-2.55(2H, m), 2.13 and 2.11(3H, s), 1.93-1.00(10H, m).

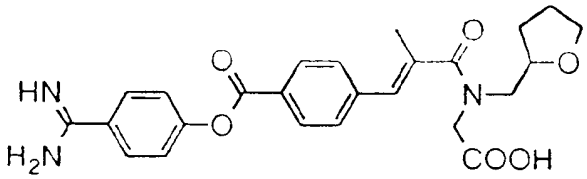
Example 2 (bb)



• AcOH

TLC : Rf 0.41 (chloroform : methanol :acetic acid = 10 : 2 : 1),
NMR (CD_3OD) : δ 8.21(2H, d, J=8Hz), 7.92(2H, d, J=8Hz), 7.65-7.50(4H, m), 6.72 and 6.65(1H, s, rotamer), 4.2-4.1 (4H, m), 3.8-3.6(2H, br), 3.6-3.5(2H, br), 3.34(3H, s), 2.17(3H, s), 1.91(AcOH), 1.35-1.15(3H, br).

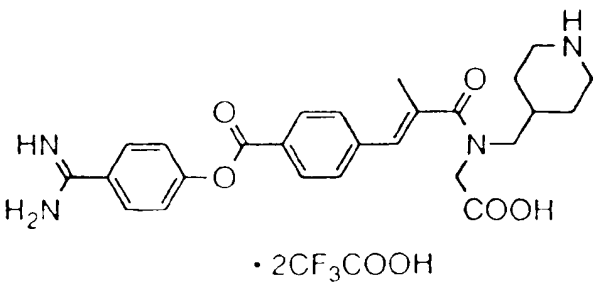
Example 2 (cc)



• MsOH

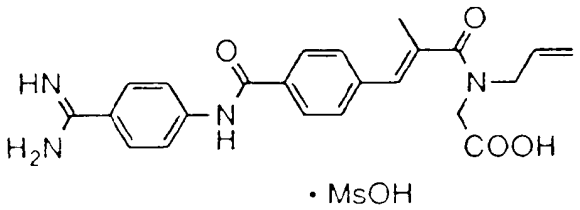
TLC : Rf 0.30 (chloroform . methanol :acetic acid = 10 : 2 : 1),
NMR (CD_3OD) : δ 8.21(2H, d, J=8Hz), 7.92(2H, d, J=8Hz), 7.60-7.45(4H, m), 6.73 and 6.65(1H, s, rotamer), 4.5-4.3 (1H, m), 4.3-4.0(2H, br), 4.0-3.7(3H, m), 3.7-3.5(1H, br), 2.70(3H, s), 2.17 and 2.10(3H, s, rotamer), 2.2-1.8(3H, m), 1.8-1.4(1H, m).

Example 2 (dd)



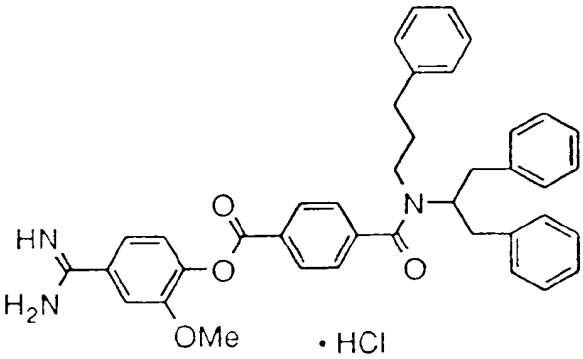
TLC : Rf 0.10 (ethyl acetate : acetic acid : H_2O = 3 : 1 : 1),
NMR (CD_3OD) : δ 8.22(2H, d, J=8Hz), 7.92(2H, d, J=8Hz), 7.7-7.4(4H, m), 6.70(1H, s), 4.5-4.0(3H, br), 3.6-3.4(2H, m), 3.2-3.0(2H, m), 2.3-1.9(7H, br)

Example 2 (ee)



TLC : Rf 0.43 (chloroform : methanol :acetic acid = 3 : 1 : 1),
NMR (CD_3OD) : δ 9.20(1H, br, s), 8.70(1H, br, s), 8.05-7.95(4H, m), 7.85(2H, d, J=9Hz), 7.75(2H, J=8Hz), 6.75(1H,m), 5.95(1H, m), 5.30(2H, m), 4.20(4H, m), 2.75(3H, s, CH_3SO_3H), 2.20(3H, s).

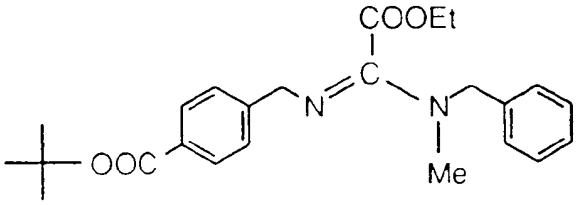
Example 2 (ff)



TLC : Rf 0.40 (chloroform : methanol : acetic acid = 10 : 2 : 1),
NMR ($CDCl_3$) : δ 8.02(1H, d, J=9Hz), 7.90(1H, d, J=9Hz), 7.64(1H, s), 7.50(1H, d, J=9Hz), 7.40-7.00(14H, m), 6.95-6.80 (2H, m), 6.80-6.72(1H, m), 6.48(1H, d, J=9Hz), 4.00-3.80(1H, m), 3.88(3H, s), 3.70-3.30,(2H, m), 3.10-2.90(1H, m), 2.90-2.70(2H, m), 2.70-2.30(2H, m), 2.30-2.00(2H, m), 1.00-1.24(1H, m)

Reference Example 3

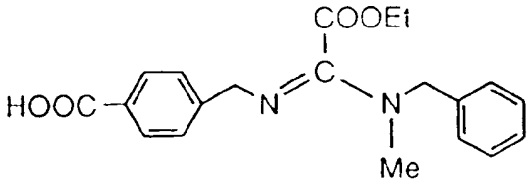
2-(N-Benzyl-N-methylamino)-2-(4-t-butoxycarbonylphenylmethylimino)acetic acid ethyl ester.



To a solution of 2-(N-benzyl-N-methylamino)-2-thioxoacetic acid ethyl ester (4.98g) in dichloromethane under cooling with ice, was added dropwise $BF_4 \cdot Et_3O$ (72ml). Reaction solution was stirred for 30min at room temperature, extracted with dichloromethane. The extract was evaporated. The residue was purified by silica gel column chromatography to give the title compound having the following the physical data.
TLC : Rf 0.45 (hexane : ethyl acetate = 3 : 1).

Reference Example 4

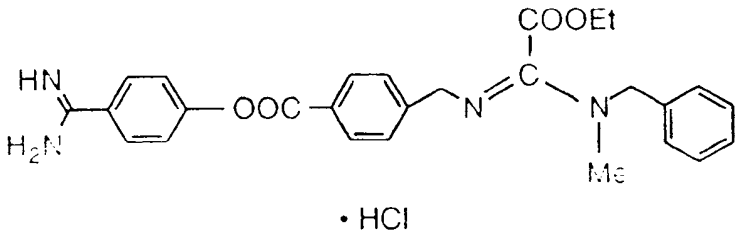
2-(N-Benzyl-N-methylamino)-2-(4-carboxyphenylmethylimino)acetic acid ethyl ester



To a solution of the compound prepared in Reference Example 3 (3.77g) in anisole (10ml) under cooling with ice bath, was added trifluoroacetic acid (20ml) and stirred for two hours at room temperature. Reaction solution was evaporated, neutralizied by adding 1N aqueous solution of sodium hydroxide and extracted with ethyl acetate. The extract was evaporated. The residue was purified by silica gel column chromatography to give the title compound (1.87g) having the following physical data.
TLC : Rf 0.36 (hexane : ethyl acetate = 1: 2).

Example 3

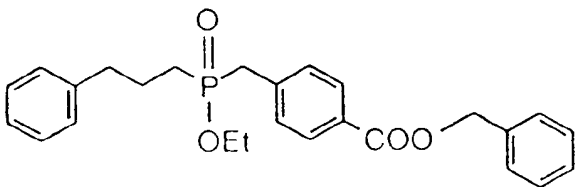
2-[4-(4-Amidinophenoxycarbonyl)phenylmethylimino]-2-(N-benzyl-N-methylamino)acetic acid ethyl ester hydrochloride



By the same procedure as Example 2, the title compound having the following physical data was given.
TLC : Rf 0.34 (chloroform : methanol :acetic acid = 10 : 2 : 1),
NMR (CD_3OD) : δ 1.26(3H, t, J=7.0Hz), 2.88(3H, s), 4.36(2H, q, J=7.0Hz), 4.49(2H, s), 4.50(2H, s), 7.27-7.35(5H, m), 7.48(2H, d, J=9.0Hz), 7.52(2H, d, J=9.0Hz), 7.92(2H, d, J=9.0Hz), 8.12(2H, d, J=9.0Hz).

Reference Example 5

Ethyl 1-(3-phenylpropyl)-1-(4-benzyloxycarbonylphenylmethyl)phosphinate.

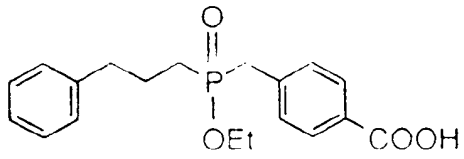


A solution of ethyl phenylpropylphosphinate (1.2g) and triethylamine (2.4ml) in chloroform (30ml) was cooled to

0°C. and a solution of trimethylsilylchloride (1.46ml) and 4-bromomethylbenzoic acid benzyl ester (1.75g) in chloroform (10ml) was added thereof, and stirred at room temperature for 1.5 day. To the reaction mixture was added ice water and extracted with ethyl acetate. Organic layer was washed with water and a saturated aqueous solution of sodium chloride, successively evaporated. The residue was purified by silica gel column chromatography to give the title compound (900mg).

Reference Example 6

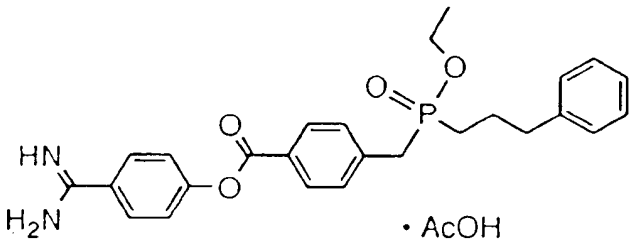
Ethyl 1-(3-phenylpropyl)-1-(4-carboxyphenylmethyl)phosphinate



A mixture of the compound prepared in Reference Example 5 (900mg), palladium carbon (180mg, 10%) and ethanol (20ml) was stirred for two hours under an atmosphere of hydrogen at room temperature. Reaction mixture was filtered. The filtrate was evaporated and the title compound (815mg) was given

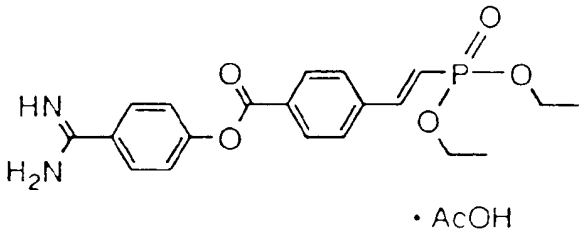
Example 4

Ethyl 1-(4-amidinophenoxycarbonylphenylmethyl)-1-(3-phenylpropyl)phosphinate acetate



By the same procedure as Reference Example 5,6 and Example 2, the title compound (805mg) having the following physical data was given.
TLC : Rf 0.62 (chloroform : methanol : acetic acid = 10 : 2 : 1),
NMR (CD_3OD) : δ 8.10(2H, d, J=8Hz), 7.95(2H, d, J=9Hz), 7.55(2H, d, J=9Hz), 7.60-7.40(2H, m), 7.30-7.10(3H, m), 7.20(2H, d, J=8Hz), 4.00(2H, m), 3.40(2H, d, J=24Hz), 2.70(2H, t, J=6.5Hz), 2.00-1.60(4H, m), 1.30(3H, t,J =7.5Hz).

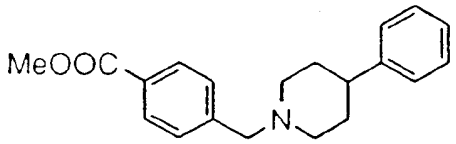
Example 4(a)



By the same procedure as Example 4, the compound having the following physical data was given.
TLC : Rf 0.60 (chloroform : methanol : acetic acid = 10 : 2 : 1),
NMR (CD_3OD) : δ 1.36(6H, t, J=7.0Hz), 4.15(4H, quin, J=7.0Hz), 6.68(1H, t, J=18.0Hz), 7.54(2H, d, J=9.0Hz), 7.56(1H, dd, J=23.0Hz,18.0Hz), 7.82(2H, d, J=9.0Hz), 7.93(2H, d, J=9.0Hz), 8.22(2H, d, J=9.0Hz).

Reference Example 7

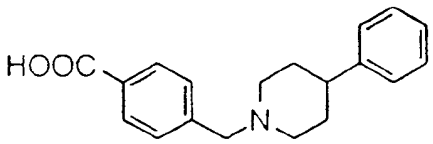
4-Phenylpiperidine-1-ylmethylbenzoic acid methyl ester



A solution of 4-formylbenzoic acid (3.5g) and 4-phenylpiperidine (6.9g) in methanol (35ml) was stirred for one hour at room temperature. After the solution was cooled with ice bath, sodium borohydride (1.63g) was added thereto and reaction solution was stirred. After reaction finished, reaction solution was poured into ice water and extracted with ethyl acetate. The organic layer was washed with water and saturated aqueous solution of sodium chloride, successively, dried over and evaporated. The residue was washed with methanol to give the title compound (4.70g).

Reference Example 8

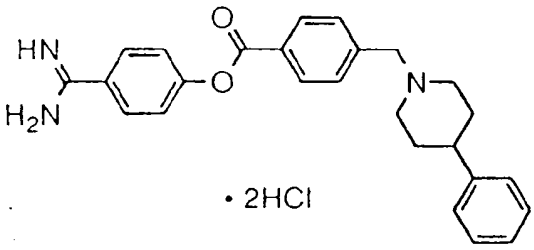
4-(4-Phenylpperidine-1-ylmethyl)benzoic acid



A solution of the compound prepared in Reference Example 7 (4.8g) in dioxane (50ml) was cooled with ice bath and 2N aqueous solution of sodium hydroxide (10ml) was added thereof and stirred at 60°C for two hours. The reaction mixture was cooled with ice bath and neutralized by adding 2N hydrochloric acid. Depositing solid was fittered and washed with water, ether successively, dried over. The title compound (4.29g) was given.

Example 5

4-(4-Phenylpiperidine-1-ylmethyl)benzoic acid amidinophenol ester 2 hydrochloride

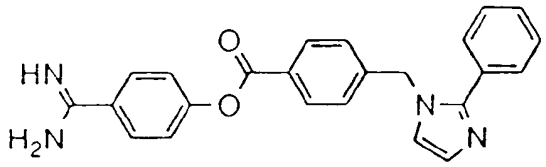


By the same procedure as Example 2, the title compound having the following physical data was given.
TLC : Rf 0.33 (chloroform : methanol : acetic acid = 5 : 1 : 1),
NMR (CD_3OD) : δ 8.32(2H, d, J=8.0Hz), 7.95(2H, d, J=8.8Hz), 7.88(2H, d, J=8.0Hz), 7.55(2H, d, J=8.8Hz), 7.28(5H, m), 4.52(2H, s), 3.62(2H, br.d), 3.25(2H, br.d), 2.94(1H, m), 2.12(4H, m).

Example 5(a)-5(b)

By the same procedure as Reference Example 7,8 and Example 5, the compound having the following physical data was given.

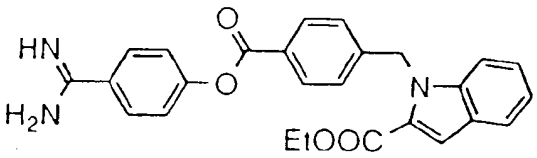
Example 5 (a)



• 2MsOH

TLC : Rf 0.3 (chloroform : methanol :acetic acid = 50 : 10 : 1),
NMR (CD_3OD) : δ 8.20(2H, d, J=8.0Hz), 7.95(2H, d, J=8.0Hz), 7.81(1H, d, J=2.0Hz), 7.79(1H, d, J=2.0Hz), 7.69(5H, brs), 7.55(2H, d, J=8.5Hz), 7.39(2H, d, J=8.5Hz), 5.63(2H, s), 2.72(6H, s).

Example 5 (b)

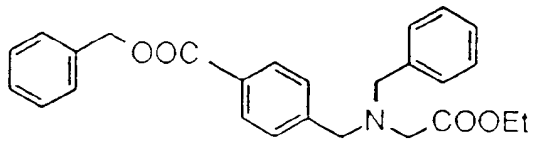


• MsOH

TLC : Rf 0.48 (chloroform : methanol : acetic acid = 10 : 1 : 1),
NMR (CD_3OD + $CDCl_3$) : δ 8.05(2H, d, J=8.4Hz), 7.89(2H, d, J=8.8Hz), 7.71(1H, d, J=8.0Hz), 7.46(2H, d, J=8.8Hz), 7.40(1H, s), 7.37-7.30(2H, m), 7.17(1H, d, J=8.0Hz), 7.16(2H, d, J=8.4Hz), 5.95(2H, s), 4.30(2H, q, J=7.4Hz), 2.73(3H, s), 1.33(3H, t, J=7.4Hz).

Reference Example 9

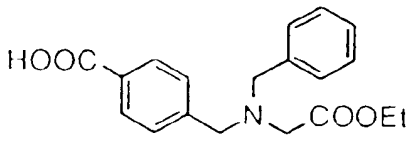
4-(N-Benzyl-N-ethoxycarbonylaminomethyl)benzoic acid benzyl ester



A solution of 4-(N-benzylaminomethyl)benzoic acid benzyl ester (5.21g) and bromoacetic acid benzyl ester (1.7ml) in DMF (10ml) was stirred for two hours at 80° C and ice water was added thereto. The reaction solution was extracted with ethyl acetate. The organic layer was washed with a saturated aqueous solution of sodium hydrogen carbonate, water and a saturated aqueous solution of sodium chloride, successively. The organic layer was dried over and evaporated. The residue was purified by silica gel column chromatography to give the title compound (2.26g).

Reference Example 10

4-(N-Benzyl-N-ethoxycarbonylaminomethyl)benzoic acid hydrochloride

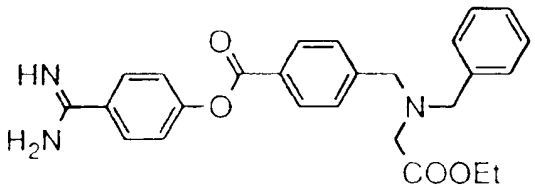


A mixture solution of the compound prepared in Reference Example 9 (2.26g), methanesufonic acid (10.5ml) and anisole (25ml)was stirred for one hour at room temperature. To the reaction solution was added ice water and extracted with chloroform. The organic layer was washed with water, a saturated aqueous solution of sodium chloride, dried over and evaporated. The residue was purified by silica gel column chromatography to give amine. 4N hydrochloric acid-di-

oxane was added to amine and the mixture was evaporated to give the title compound (1.76g)

Example 6

N-(4-(4-Amidino-phenoxycarbonyl)phenylmethyl)-N-benzylaminoacetic acid ethyl ester 2 hydrochroride



• 2HCl

By the same prodedure as Example 2, the title compound having the following physical data was given.
TLC : Rf 0.42 (chloroform : methanol : acetic acid = 10 : 2 : 1),
NMR (CD_3OD) : δ 8.25(2H, d, J=8Hz), 7.90(2H, d, J=8Hz), 7.60(2H, d, J=8Hz), 7.50(2H, d, J=8Hz), 7.40-7.20(5H, m), 4.15(2H, q, J=7Hz), 3.90(2H, s), 3.80(2H, s), 3.30(2H, s), 1.25(3H, t, J=7Hz).

Formulation Example 1

The following components were admixed in conventional manner and punched out to obtain 100 tables each containing 100mg of active ingredient.

Compound number 1	10g
Cellulose calcium glycolate (disintegrating agent)	0.2g
Magnesium stearate (Lubricating agent)	0.1g
Microcrystaline cellulose	1.7g

Formation Example 2

The following components were admixed conventional method and punched out to obtain 100 tables each containing 100mg of active ingredient.

Compound number 2	10g
Cellulose calcium glycolate (disintegrating agent)	0.2g
Magnesium stearate (Lubricating agent)	0.1g
Microcrystaline cellulose	1.7g

Formation Example 3

The following components were admixed in conventional manner. The solution was sterilized conventional manner, placed 5ml portions into 10ml ampoules and obtained 100 ampoules each containing 10mg of the active ingredient.

Compound number 1	1g
Citric acid	0.2g
distilled water	500ml

Formation Example 4

The following components were admixed in conventional manner. The solution was sterilized in conventional manner, placed 5ml portions into 10ml ampoules and obtained 100 ampoules each containing 10mg of the active ingredient.

Compound number 2	1g

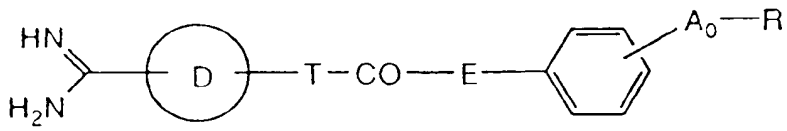
Continuation of the Table on the next page

(continued)

Citric acid	0.2g
distilled water	500ml

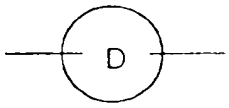
Claims

1. An amidinophenol derivative of the formula (IB):



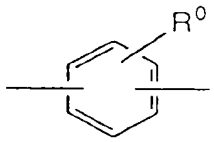
(IB)

wherein:

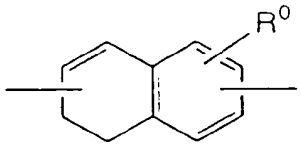


is a group of the formula :

(i)

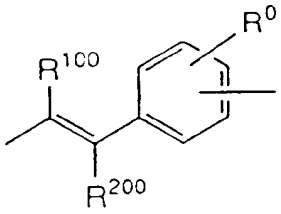


(ii)

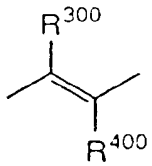


or

(iii)

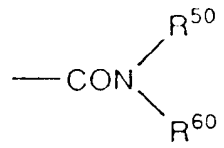


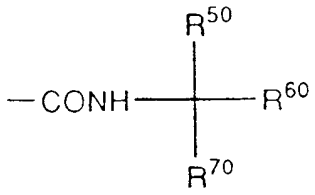
(in which R^0 is hydrogen, or C1-4 alkyl, or C1-4 alkoxy),
T is NH or oxygen,
E is a single bond, or
a group of the formula :

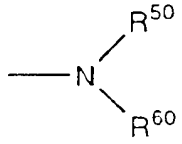


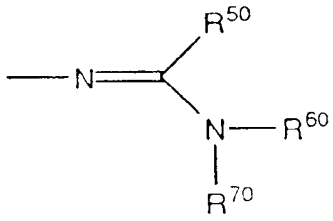
A_0 is a single bond, C1-4 alkylene, -oxy-(C1-4)alkylene-, -thio-(C1-4)alkylene-, C2-8 alkenylene, or C2-8 alkenylene which is substituted by carboxy or by C1-4 alkoxycarbonyl. R^{100}, R^{200}, R^{300} and R^{400} each independently, is hydro-

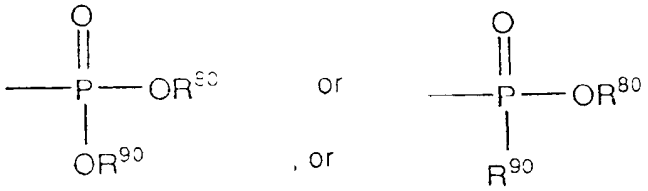
gen or C1-4 alkyl, R is a group of the formula:

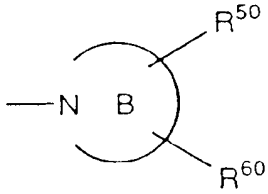
(i) 

(ii) 

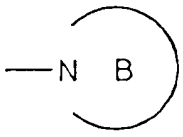
(iii) 

(iv) 

(v) 

(vi) 

(in which the grouping:



is a 4-10 membered hetero ring containing one or two nitrogen atoms),
R^{50}, R^{60} and R^{70} each independently, is,

(i) hydrogen,

(ii) C1-8 alkyl,

(iii) C2-8 alkenyl,

(iv) -$COOR^{110}$ (in which R^{110} is hydrogen or C1-4 alkyl unsubstituted or substituted by phenyl),

(v) -(C1-8 alkylene)-$COOR^{110}$ (in which R^{110} has the same meaning as hereinbefore defined),

(vi) -(C2-8 alkenylene)-$COOR^{110}$ (in which R^{110} has the same meaning as hereinbefore defined),

(vii) C4-7 cycloalkyl,

(viii) -(C1-4 alkylene)-(4-7 membered hetero ring containing one oxygen),

(ix) -(C1-4 alkylene)-(4-7 membered hetero ring containing one nitrogen),

(x) phenyl,

(xi) C1-8 alkyl which is substituted by one or two phenyl,

(xii) -(C1-4 alkylene)-O-benzoyl,

(xiii) -(C1-4 alkylene)-CONH-(C1-4 alkylene)-$NR^{120}R^{130}$,

(xiv) -(C1-4 alkylene)-COO-(C1-4 alkylene)-$NR^{120}R^{130}$,

(xv) -(C1-4 alkylene)-COO-amidinophenyl,

(xvi) -(C1-4 alkylene)-CONH-(C1-4 alkyl which is substituted by one or two -$COOR^{110}$) (in which R^{110} has the same meaning as hereinbefore defined),

(xvii) -(C1-4 alkylene) -$CONR^{120}R^{130}$, or

(xviii) (C1-4) alkoxy (C1-4) alkyl; R^{80} and R^{90} each independently, is C1-4 alkyl or -(C1-4 alkylene)-phenyl, R^{120} and R^{130} each independently, is hydrogen, C1-4 alkyl, or C2-8 alkenyl,

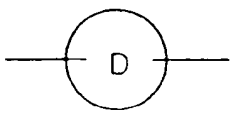
with the provisos that:

(1) R^{50} and R^{60} in the formulae (i) and (iii), and R^{50}, R^{60} and R^{70} in the formulae (ii) and (iv), do not represent hydrogen at the same time,

(2) when at least one substituent in R^{50}, R^{60}, R^{70} and A_0 represent substituent containing -COO-t-Bu, the other groups do not represent groups containing carboxy,

(3) R^{120} and R^{130} do not represent hydrogen at the same time,

(4) when
T is oxygen,
the grouping:



is the formula (i) as hereinbefore described,
E is a single bond,
A_0 is a single bond, C1-4 alkylene or vinylene which is optionally substituted by one or two C1-4 alkyl, and
R is the formula (i) as hereinbefore described,
then at least one group in R^{50}, R^{60} and R^{70} is

(viii) -(C1-4 alkylene)-(4-7 membered hetero ring containing one oxygen),

(ix) -(C1-4 alkylene)-(4-7 membered hetero ring containing one nitrogen),

(x) phenyl,

(xi) C1-8 alkyl which is substituted by one or two phenyl,

(xii) -(C1-4alkylene)-O-benzoyl,

(xiii) -(C1-4 alkylene)-CONH-(C1-4 alkylene)-$NR^{120}R^{130}$,

(xiv) -(C1-4 alkylene)-COO-(C1-4 alkylene)-$NR^{120}R^{130}$,

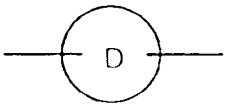
(xv) -(C1-4 alkylene)-COO-amidinophenyl,

(xvi) -(C1-4 alkylene)-CONH-(C1-4 alkyl which is substituted by one or two -$COOR^{110}$) (in which R^{110} has the same meaning as hereinbefore defined),

(xvii) -(C1-4 alkylene)-$CONR^{120}R^{130}$, or

(xviii) -(C1-4)alkoxy(C1-4)alkyl;

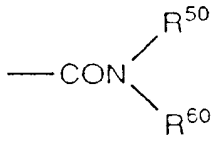
(5) when
T is oxygen,
the formula :



is the formula (i) as hereinbefore defined,
E is bond,
A_0 is bond, C1-4 alkylene or vinylene which may be optionally substituted by one or two C1-4 alkyl, and R is the formula (ii) as hereinbefore defined,
then R^{50}, R^{60} and R^{70} do not represent hydrogen;
or a non-toxic salt thereof or a non-toxic acid addition salt thereof.

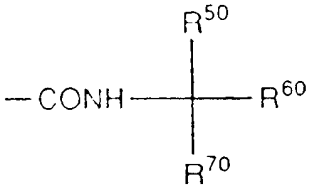
2. A compound according to claim 1,wherein R is

(i)



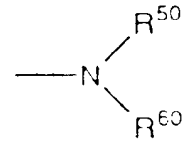
or

(ii)

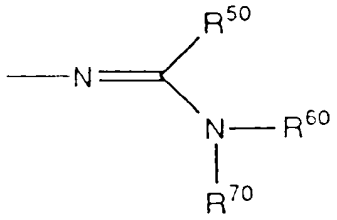


in which the various symbols are as defined in claim 1.

3. A compound according to claim 1, wherein R is

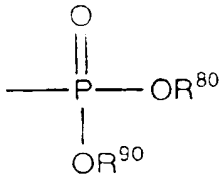
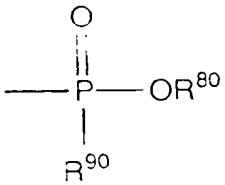
(iii) 

or

(iv) 

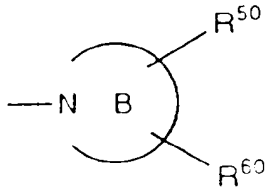
in which the various symbols are as defined in claim 1.

4. A compound according to claim 1, wherein R is

(v)  or 

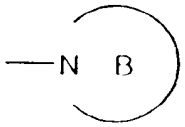
in which the various symbols are as defined in claim 1.

5. A compound according to claim 1, wherein R is

(vi) 

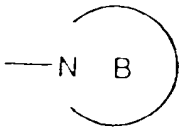
in which the various symbols are as defined in claim 1.

6. A compound according to claim 1, wherein



is a 4-10 membered hetero ring containing one nitrogen.

7. A compound according to claim 1, wherein



is a 4-10 membered hetero ring containing two nitrogen.

8. A compound according to claim 1, wherein R^{50}, R^{60} and R^{70} each independently, is

(i) hydrogen.

(ii) C1-8 alkyl,

(iii) C2-8 alkenyl,

(iv) -$COOR^{110}$,

(v) -(C1-8 alkylene)-$COOR^{110}$,

(vi) -(C2-8 alkenylene)-COOR110,

(vii) C4-7 cycloalkyl,

(x) phenyl,

(xi) C1-8 alkyl which is substituted by one or two phenyl,

(xii) -(C1-4 alkylene)-O-benzoyl,

(xiii) -(C1-4 alkylene)-CONH-(C1-4 alkylene)-$NR^{120}R^{130}$,

(xiv) -(C1-4 alkylene)-COO-(C1-4 alkylene)-$NR^{120}R^{130}$,

(xv) -(C1-4 alkylene)-OCO-amidinophenyl,

(xvi) -(C1-4 alkylene)-CONH-(C1-4 alkyl which is substituted by one or two -$COOR^{110}$),

(xvii) -(C1-4 alkylene)-$CONR^{120}R^{130}$, or

(xviii) -(C1-4)alkoxy(C1-4)alkyl, in which the various symbols are defined in claim 1.

9. A compound according to claim 1, wherein R^{50}, R^{60} and R^{70} each independently, is (viii) -(C1-4 alkylene) -(4-7 membered hetero ring containing one oxygen).

10. A compound according to claim 1, wherein R^{50}, R^{60} and R^{70} each independently, is (ix) -(C1-4 alkylene)- (4-7 membered hetero ring containing one nitrogen).

11. A compound. according to claim 1, which is
4-(4-amidinophenoxycarbonyl)phenoxyacetic acid N-2-propenyl-N-ethoxycarbonylmethylamide,
4-(6-amidino-7,8-dihydro-2-naphthyloxycarbonyl)benzoic acid N-phenyl-N-phenylmethylamide,
4-(6-amidino-7,8-dihydro-2-naphthyloxycarbonyl)benzoic acid N-phenyl-N-benzyloxycarbonylmethylamide,
4-(6-amidino-7,8-dihydro-2-naphthyloxycarbonyl)benzoic acid N-phenyl-N-ethoxycarbonylmethylamide,
4-[4-(2-amidinoethenyl)phenoxycarbonyl]benzoic acid N-phenyl-N-ethoxycarbonylmethylamide,
4-(4-amidinophenoxycarbonyl)-α-methylcinnamic acid N-1-(S)-ethoxycarbonyl-2-benzoyloxyethylamide,
4-[2-(4-amidinophenoxycarbonyl)ethenyl]benzoic acid N-1-(S), 3-bis(ethoxycarbonyl)propylamide,
4-[2-(4-amidinophenoxycarbonyl)-1-propenyl]benzoic acid N-1-(S), 3-bis(ethoxycarbonyl)propylamide,
4-(4-amidinophenoxycarbonyl)-α-methylcinnamic acid N-[1, 1, 4-tris(ethoxycarbonyl)-3-butenyl]amide,
4-[4-(2-amidinoethenyl)phenoxycarbonyl]benzoic acid N-ethoxycarbonylmethyl-N-allylamide,
4-(4-amidinophenoxycarbonyl)phenoxyacetic acid N-1-(S), 3-bis(ethoxycarbonyl)propylamide,
4-(4-amidinophenoxycarbonyl)-α-methylcinnamic acid N-1, 1, 2-tris(ethoxycarbonyl)ethylamide,
4-[2-(4-amidinophenoxycarbonyl)-1-propenyl]benzoic acid N-ethoxycarbonylmethyl-N-allylamide,
5-[4-(4-amidinophenoxycarbonyl)phenyl]-2, 4-pentadienoic acid N-1-(S), 3-bis(ethoxycarbonyl)propylamide,
5-[4-(4-amidinophenoxycarbonyl)phenyl]-2, 4-pentadienoic acid N-ethoxycarbonylmethyl-N-allylamide,
4-(4-amidinophenoxycarbonyl)-α-methylcinnamic acid N-[1, 1-bis(ethoxycarbonyl)-3-butenyl]amide,
4-[2-(4-amidinophenoxycarbonyl)-1-methylethenyl]benzoic acid N-1-(S), 3-bis(ethoxycarbonyl)propylamide,
4-[2-(4-amidinophenoxycarbonyl)-1-methylethenyl]benzoic acid N-ethoxycarbonylmethyl-N-allylamide,
3-[4-(4-amidinophenoxycarbonyl)phenyl]-2-ethoxycarbonyl-2-propenoic acid N-1-(S), 3-bis(ethoxycarbonyl)propylamide,
3-[4-(4-amidinophenoxycarbonyl)phenyl]-2-ethoxycarbonyl-2-propenoic acid N-ethoxycarbonylmethyl-N-allyla-

mide,
4-(4-amidinophenoxycarbonyl)-α-methylcinnamic acid N-2-dimethylaminoethylcarbamoylmethyl-N-allylamide,
4-(4-amidinophenoxycarbonyl)-α-methylcinnamic acid N-2-dimethylaminoethoxycarbonylmethyl-N-allylamide,
4-(4-amidinophenoxycarbonyl)-α-methylcinnamic acid N-4-amidinophenoxycarbonylmethyl-N-allylamide,
4-(4-amidinophenoxycarbonyl)-α-methylcinnamic acid N-1, 1- bis(ethoxycarbonyl)methylcarbamoylmethyl-N-allylamide,
4-(4-amidinophenoxycarbonyl)-α-methylcinnamic acid N-(diallylcarbamoyl)methyl-N-allylamide,
4-(4-amidinophenoxycarbonyl)-α-methylcinnamic acid N-(1-(S)-ethoxycarbonyl-3-methylbutyl)-N-ethoxycarbonylmethylamide,
4-(4-amidinophenoxycarbonyl)-α-methylcinnamic acid N-3-methylbutyl-N-2-(ethoxycarbonyl)ethylamide,
4-(4-amidinophenoxycarbonyl)-α-methylcinnamic acid N-cyclohexyl-N-2-carboxyethylamide,
4-(4-amidinophenoxycarbonyl)-α-methylcinnamic acid N-2-methoxyethyl-N-ethoxycarbonylmethylamide,
4-(4-amidinophenylcarbamoyl)-α-methylcinnamic acid N-allyl-N-carboxymethylamide, or
4-(4-amidino-1-methoxyphenoxycarbonyl)benzoic acid N-1, 1-bis(phenylmethyl)methyl-N-3-phenylpropylamide.

12. A compound according to claim 1, which is
2-[4-(4-amidinophenoxycarbonyl)phenylmethylimino]-2-(N- benzyl-N-methylamino)acetic acid ethylester, or
2-{N-[4-(4-amidinophenoxycarbonyl)phenyl]methyl-N-benzylamino}acetic acid ethyl ester.

13. A compound according to claim 1, which is
ethyl 1-[4-(4-amidinophenoxycarbonyl)phenylmethyl]-1-(3-phenylpropyl)phosphinate, or
diethyl 2-[4-(4-amidinophonoxycarbonyl)phenyl]-ethenylphosphonate.

14. A compound according to claim 1, which is
4-(4-amidionophenoxycarbonyl)-α-methylcinnamic acid N-(2,3,4,5-tetrahydro-fran-2-yl)methyl-N-carboxymethylamide.

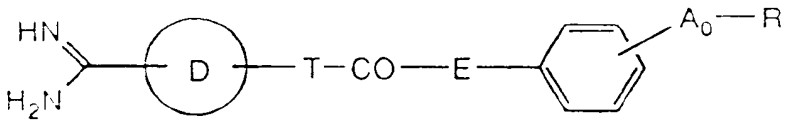
15. A compound according to claim 1,which is
4-(4-amidinophenoxycarbonyl)-α-methylcinnamic acid N-(4-piperidinylmethyl)-N-carboxymethylamide.

16. A compound according to claim 1, which is
4-(4-phenylpiperidinylmethyl)benzoic acid 4-amidinophenyl ester, or
4-(2-ethoxycarbonylindolylmethyl)benzoic acid 4-amidinophenyl ester.

17. A compound according to claim 1, which is
4-(2-phenylimidazolylmethyl)benzoic acid 4-amidinophenyl ester.

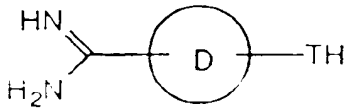
18. A compound according to any one of the preceding claims in the form of a non-toxic acid addition salt.

19. A process for the preparation of a compound of formula (IB) :

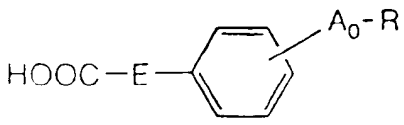


(IB)

which comprises the reaction to form an ester or amide bond, of a compound of the formula:



(wherein the various symbols are as defined in claim 1)
with a compound of the formula :

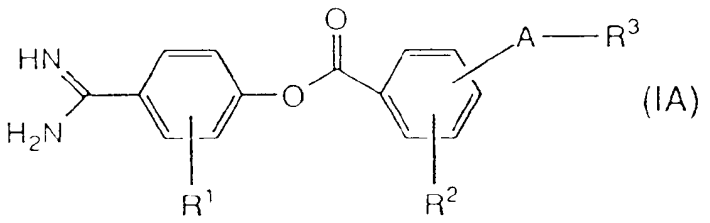


(wherein the various symbols are as defined in claim 1); and optionally converting the amidinophenol derivative thus obtained into a salt or acid addition salt thereof.

20. A pharmaceutical composition which comprises, as active ingredient, an amidinophenol derivative of the formula (IB) depicted in claim 1, or a non-toxic salt thereof, or non-toxic acid addition salt thereof, with a carrier or coating.

21. An amidinophenol derivative of the formula (IB) depicted in claim 1, a non-toxic salt thereof or non-toxic acid addition salt thereof for use in the manufacture of a medicament for treatment of a condition which can be ameliorated by the administration of a leukotriene B_4 antagonist or by an inhibitor of phospholipase A_2 or trypsin.

22. A compound of the formula (IA) :



(IA)

wherein R^1 and R^2 each independently, is:

(i) hydrogen, or

(ii) $-COOR^4$ (in which R^4 is C1-3 alkyl);

A is

(i) a single bond,

(ii) C1-4 alkylene, or

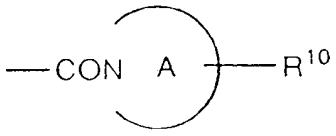
(iii) $-C(R^5)=C(R^6)-$ (in which R^5 and R^6 each independently, is hydrogen or C1-4 alkyl);

R^3 is

(i) $-CON(R^7)R^8$,

(ii) $-CONR^9-CH(R^7)R^8$, or

(iii)



(wherein R^7 and R^8 each independently, is

(1) hydrogen,

(2) phenyl,

(3) -(C1-4 alkylene)-phenyl,

(4) -(C1-4 alkylene)-phenyl which is substituted by one or two $-R^{11}-COOR^{12}$
(in which R^{11} is a single bond or C1-8 alkylene, and R^{12} is hydrogen or C1-4 alkyl),

(5) C1-5 alkyl,

(6) C2-10 alkenyl containing one to three double bonds,

(7) -R^{11a}-$COOR^{12}$
(in which R^{11a} is

(a) a single bond,

(b) C1-8 alkylene,

(c) C2-8 alkenylene, or

(d) C4-8 alkenylene in which one or two carbon atoms in the main chain are replaced by sulfur, and R^{12} has the same meaning as hereinbefore defined), or

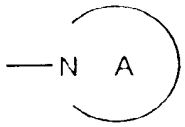
(8) C3-7 cycloalkyl;

R^9 is

(1) hydrogen,

(2) -R^{11}-$COOR^{12}$ (in which the various symbols have the same meanings as hereinbefore defined), or

(3) C2-6 alkoxyalkyl;
the grouping



is a 4-7 membered mono hetero ring contain one or two nitrogen;

R^{10} is

(1) hydrogen, or

(2) -(C1-4 alkylene)-phenyl,
with the proviso that:

(1) both R^7 and R^8 do not represent hydrogen at the same time,

(2) when at least one group in R^7, R^8, and R^9 represent the group containing -COO-t-Bu, the other groups do not represent the groups containing carboxy;

a non-toxic salt thereof or non-toxic acid addition salt thereof for use in the manufacture of a medicament for the treatment of a condition which can be ameliorated by the administration of an LTB_4 antagonist.

23. An amidinophenol derivative of the formula (IA) depicted in claim 24, a non-toxic salt thereof or a non-toxic acid addition salt thereof for use in the manufacture of a medicament for the treatment of an allergic or inflammatory condition which can be ameliorated by the administration of an LTB_4 antagonist

09/737687

European Patent Office

EUROPEAN SEARCH REPORT

Application Number
EP 95 30 6596

DOCUMENTS CONSIDERED TO BE RELEVANT

Category	Citation of document with indication, where appropriate, of relevant passages	Relevant to claim	CLASSIFICATION OF THE APPLICATION (Int.Cl.6)
D,X	EP-A-0 588 655 (ONO PHARMACEUTICAL CO. LTD.) * whole document *	1-3,5-8, 10,19-23	C07C257/18 C07C257/14 C07D211/14 A61K31/155
X	BIOMEDICAL RESEARCH, vol.15, no.1, January 1994, TOKYO, JP pages 55 - 8 A. MATSUSHIMA ET. AL. 'Inhibition of a mite protease (Df protease) by synthetic inhibitors' * whole document *	1-3,5-8, 18-23	
A	EP-A-0 048 433 (TORII & CO. LTD.) * claims; examples *	1-23	
A	FR-A-2 556 720 (TORII & CO. LTD.) * claims; examples *	1-23	
A	CH-A-520 657 (DR. A. WANDER AG) * whole document *	1-23	
P,X	EP-A-0 656 349 (ONO PHARMACEUTICAL CO. LTD.) * whole document *	1-23	
T	JOURNAL OF MEDICINAL CHEMISTRY., vol.38, no.22, 27 October 1995, WASHINGTON US pages 4508 - 17 K. SENOKUCHI ET. AL. 'New Orally Active Serine Protease Inhibitors: Structural Requirements for Their Good Oral Activity' * whole document *	1-23	

TECHNICAL FIELDS SEARCHED (Int.Cl.6)
C07C
C07D

The present search report has been drawn up for all claims

Place of search	Date of completion of the search	Examiner
THE HAGUE	19 January 1996	Helps, I

CATEGORY OF CITED DOCUMENTS

X : particularly relevant if taken alone
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